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SERMENT

En présence des Maîtres de la Faculté, des Conseillers de l'Ordre des Pharmaciens et de mes condisciples, je jure :

D'honorer ceux qui m'ont instruit dans les préceptes de mon art et de leur témoigner ma reconnaissance en restant fidèle à leur enseignement.

D'exercer, dans l'intérêt de la santé publique, ma profession avec conscience et de respecter non seulement la législation en vigueur, mais aussi les règles de l'honneur, de la probité et du désintéressement.

De ne jamais oublier ma responsabilité et mes devoirs envers le malade et sa dignité humaine.

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Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

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LIST OF ABBREVIATIONS

5-CNAC: N-[8-(5-chlorosalicyloyl)-amino] caprylic acid

ADAs: Anti-drug antibodies

B2B: Business to Business

BLA: Biologics License Applications

CAGR: Compound annual growth rate

CDER: Center for Drug Evaluation & Research

CFR: Code of Federal Regulations

c GMP: Cyclic guanosine monophosphate

CIC: Chronic Idiopathic Constipation

FDA: Food and Drug Administration

FNS: Flexible needle Shield

GERD: Gastro esophageal Reflux Disease

GI: Gastro-intestinal

GIPET: Gastrointestinal Permeation Enhancement Technology

GLP1: Glucagon-like peptide-1

HLB: Hydrophilic-Lipophilic Balance

IBS-C: Irritable Bowel Syndrome with Constipation

IM: Intramuscular

INDs: Investigational New Drug

IV: Intravenous

LRH: Luteinizing hormone-releasing hormone

MW: Molecular weight

NCOA: National council on aging

NDA: New Drug Application

NS: Needle Shield

PEG: Polyethylene glycol

PFS: Prefillable Syringe

PLGA: Polylactic co glycolic acid

POD: Protein Oral Delivery

PSA: Polysialic acid

PTH: Parathyroid hormone

RNS: Rigid needle Shield

SAIS: Self-Administration Injection Systems

SbVPs: Sub visible particles

SC: Subcutaneous

SLEPT: Social, Legal, Economic, Political, Technological

SNAC: Monosodium N-[8-(2-hydroxybenzoyl) amino] caprylate

TCO: Total Cost of Ownership

TERNS: Proprietary Thermoplastic Elastomer Rigid Needle Shield

TPE: Transient permeability enhancer

TRH: Thyrotropin-releasing hormone

GLOSSARY

Biologic: A medicinal preparation made from living organisms.

Biosimilars: Biosimilars are a type of biological products, highly similar to an already FDA-approved biological product (the reference product), that have been shown to have no clinically meaningful differences from the reference product.

Combination products: Product comprised of two or more regulated components such as drug/device, biologic/device that are combined and produced as a single entity.

Formulation: The formulation of a medicine is the way in which different ingredients are combined to make it.

Generic drug: A generic drug is bioequivalent and chemically identical to a brand name drug (dosage form, route of administration, performance characteristics, etc.). Most of the time, its price is lower than the brand name drug.

Paracellular transport: This is the transport of a drug across an epithelium, by passing through the intercellular space between the cells.

Parenteral route of administration: The parenteral route is defined as a route other than through the alimentary canal (contrary to the enteral route), such as by subcutaneous, intramuscular or intravenous injection.

Pharmacokinetic: Pharmacokinetic is the study of the movements of a drug in the body including the process by which a drug is absorbed, distributed, metabolized and eliminated.

Pharmacological half-life: The half-life of the molecule corresponds to the duration of action of a drug. It represents the period of time required for the amount of drug in the body to be reduced by one-half.

Syringeability: The ability of a product to be successfully administered by a syringe.

TCO: Direct and indirect costs of a product

Transcellular transport: This is the transport of a drug across an epithelium, by passing through the apical membrane and the basolateral membrane of an epithelial cell.

Vaccine: A vaccine is a biological preparation made of killed or weakened germs, injected into the body. The purpose of this injection is to trigger the formation of antibody (proteins that is involved in the body's active defence). In other words, a vaccine is characterized by a germ which has lost its virulence and that stimulates the immune system.

I. INTRODUCTION

Small molecules dominate the global pharmaceutical market (75%) (1). However, the percentage share of biologic-based drugs grows and is expected to continue increasing. This can be explained by the interesting features of those molecules: the high specificity and selectivity that open the doors to develop therapies in areas of high medical unmet needs (polyarthritis for example).Biologics are manufactured in living systems such as a microorganism, plant or animal cells. They have a complex structure leading to unacceptably low oral bioavailability. Therefore, biologics must be administered parenterally through intramuscular injection, subcutaneous injection or infusion. The trend to home treatment and self-administration encourages the use of combination products of prefilled syringes (PFS) with safety and Self-Administration Injection Systems (SAIS) devices or cartridges with pens for injectable drugs. However, the parenteral administration still raises convenience concerns. Therefore, pharmaceutical companies are increasingly interested in alternative routes of administration.

Different solutions have been explored by pharmaceutical companies in order to enhance treatment adherence and thus the therapeutic outcomes. Among all the technology under development, the oral delivery of biologics seems to offer lots of benefits and could become a disruptive innovation in the market. Oral delivery is regarded as the safest, most convenient and most economical method of drug administration, and patient acceptance and compliance are typically higher when medicines are delivered orally. There is currently no biologics that are administered orally on the market. However, this route of administration has a tremendous commercial potential. Recently, J&J hosted an oral biologics startup at its new incubator to help it find REMICADE®'s replacement (2). Novartis partners with Rani Therapeutics' novel oral biologics delivery system. The pharmaceutical company also invested in Series C financing round of Rani Therapeutics worth a total of more than $25 million (3). It should also be noted that Venture capitalists are betting big on oral biologics (4): more than 100 venture backed companies are currently working on oral delivery mechanism for biologics (4).

The ultimate objective of this thesis is to determine the current challenges and trends in the field of biologic drug delivery, to identify and evaluate the scientific platforms that aim to develop biologics via oral administration and to determine the potential impact of these new technologies on the drug delivery system market.

II. Context and interest of the subject

Biologics are increasingly popular as they allow targeting specific sites with high selectivity. Thanks to these features, biologics have been developed to treat diseases with high medical unmet needs. This is the case, for example, of the polyarthritis. Biologics have become an important part of the pharmaceutical pipeline: each year, more Investigational New Drug (INDs) applications are requested (5). In 2015, 12 biologics have received a biologic license application (BLA) by the Food and Drug Administration (FDA): VONVENDI®, FLUAD®, ADYNOVATE®, (6) etc. Biologics represent an interesting opportunity for pharmaceutical companies as they can't be systematically substituted by generics at the patent expiry contrary to small molecules. Moreover, the regulatory requirements for biosimilars are more stringent compared with generics meaning that there is a supplementary barrier to develop biosimilars. No clinically meaningful differences from the reference product have to be demonstrated.

In 2004, most of the world's top ten selling products were small molecules; today, only few small molecules are still included in the top ten selling products (see table 1) (7).

Table 1 : Worldwide product sales, 2004-2014 (USD millions) (7)

	2004		2009		2014	
Product rank	Product	Sales (USD millions)	Product	Sales (USD millions)	Product	Sales (USD millions)
1	Lipitor	11.727	Lipitor	12.651	Humira	12.543
2	Zocor	5.197	Plavix	9.455	Solvadi	10.283
3	Plavix	5.110	Enbrel	8.489	Remicade	9.916
4	Norvasc	4.463	Advair	7.792	Enbrel	8.949
5	Zyprexa	4.420	Abilify	6.600	Lantus	8.435
6	Advair	4.382	Remicade	6.419	Abilify	8.404
7	Nexium	4.019	Diovan	6.091	Rituxan	7.553
8	Pravachol	3.679	Avastin	5.745	Advair	7.035
9	Epogen	3.589	Rituxan	5.620	Avastin	7.023
10	Prevacid	3.455	Humira	5.563	Herceptin	6.868
	Total	**50.041**		**74.425**		**87.009**

During the last decade, the development of new routes of administration for biologics has emerged within the biopharmaceutical industry (for example inhaled insulin; Exubera® (8), etc.). These new ways of delivering biologics could have an impact on the current drug delivery market. The purpose of this thesis is to get a better understanding of the current challenges in the field of delivery methods for biologics in order to determine what could be the potential interest of alternative methods. The objectives are also to identify the new technologies that mean needle-free delivery methods in order to relevantly position those technologies in the future market.

A better understanding of the current offer regarding biologics delivery supported with a better understanding of the formulation/administration related issues will allow determining the benefits of the technologies currently under development and the potential impact of these technologies on the future market.

To set up this landscape analysis, technologies under development and key players need to be defined, described and evaluated. Key players should be identified, characterized and evaluated to determine what their chance to succeed is. The impact of these technologies on the drug delivery market will be determined.

III. Material and Methods

III.1. Methodology

To conduct properly a market analysis, there are different steps that need to be followed. The first one is to determine the goals and the objective of the research. Concerning this research, the main objectives were to be able to identify the current challenges in the field of biologics delivery and the trends related to administration of biologics. In parallel, the new technologies under development that aim to deliver biologics orally had to be characterized. The second step was to define the decision problem to be studied via a market research to better identify which information are required to answer our question.

Once that had been done, the data collection process could begin. Gathering the information implies that the source of data had been previously identified (internal and external data source). The last step is to analyze of the data gathered.

III.2. Research questions

The questions that will be explored during the research will be the following:

What are the key trends and unmet customer needs in the delivery of biologics?

In order to answer this question, it is first important to define the market and the current challenges in the field of administration and formulation of biologics. Then the following questions will be explored:

- How is the healthcare landscape evolving?
- What technologies exist and what may come onto the market?
- Based on the above trend, what is the integrated story of this market?

What are the current and future boundaries of our market?

- Where do the existing products fit within the market?
- How large are these various opportunities within the market?

Which technology or company seems to have the greatest chance of being a disruptive force in the industry?

III.2.a. Data source

The goals were to identify the current challenges throughout the formulation and administration of biologics but also to determine the current boundaries in order to isolate the emerging trends. To do so, the issues linked to the development of biologics will be defined to highlight the unmet need of pharmaceutical companies. It will also include an analysis concerning the complexity of injectable formulations and delivery devices designed for biologics.

As the goals and objectives were well-identified and the decision problem defined, the next step was to determine which data source could be relevant and useful to conduct the research. Scientific review and specialized literature will enable to understand the trends within the biopharmaceutical companies. The scientific database will also provide relevant information to understand the biologics market and the boundaries of current delivery devices. The technology under development will be identified through press releases, scientific reviews and scientific database (for example PubMed, med track).

Professionals working on biologics development will be contacted using professional social networks such as LinkedIn and seminar agenda related to biologics formulation. Interviews with Scientifics working on biologics formulations will be organized to evaluate these technologies and determine their chance of success. Those interviews will allow the gathering of qualitative information (therefore, no specific survey will be developed; the questions will depend on the expertise of the interviewee). Regarding the results, assumptions and recommendations will be made.

III.2.b. Spacio-temporal framework

This thesis will mainly focus on Western Europe and will be based on data from 2014.

III.2.c. Market framework

The thesis will be focused on the glass PFS market for biologics. Plastic PFS used to deliver biologics is considered as a minor market (especially in US and Europe) and will not be explored in the report. The vaccine delivery device will also be excluded from the analysis as they have their own features which differ from biotech delivery devices (route of administration, luer lock syringes, etc.).

IV. Background

IV.1. Biologics

IV.1.a. Definition

Biologics are defined by FDA as follows: "Biological products, or biologics, are medical products. Many biologics are made from a variety of natural sources (human, animal or microorganism). Like drugs, some biologics are intended to treat diseases and medical conditions. Other biologics are used to prevent or diagnose diseases". As previously said, biologics are produced by cutting-edge technologies from natural sources such as microorganism, plants, humans or animals (9). Biologics are complex molecules which differ from chemical drugs. Three main differences can be identified:

- First, the manufacturing involves use of living systems (bacteria, yeast, viruses…). These systems must be kept alive in a controlled environment to allow the efficient production of the desired protein with the appropriate quality.
- Second, the manufacturing process has a significant impact on the final product. Contrary to small molecules produced via chemical synthesis which are well-defined, it is difficult to characterize biologics as they have a complex structure and are derived from biological sources. Therefore, the product is characterized by the process itself. Contrary to small molecules, the manufacturing process of a biologics should remain the same over time in order to ensure the product quality and consistency.
- Third, the complex structure of the drug requires appropriate test methods for their analysis increasing the challenge for Quality Control. (10)

These major differences between small molecules and biologics explain why regulatory authorities manage the biologics differently (11). Follow on biological products which are not considered to be generic drugs are called biosimilars.

Biosimilars have more constraints regarding the clinical trials comparing with generics. Once again, this is mainly due to the complex structures and the potential immunogenicity of these drugs (12). Indeed, non-human proteins are recognized as foreign, and can induce an adaptive immune response leading to a decreased efficacy of the biologics. This is particularly true for monoclonal antibodies with a murine origin. With the development of chimeric, humanized and

fully human mAbs, monoclonal antibodies are thought to be less immunogenic, however, it has been shown that even fully human can be immunogenic (13).

IV.1.b. Classification

The biologics can by classified into different ways. A first way is to classify the product regarding the pharmacology: cytokine, monoclonal antibodies, enzymes, etc. If we take the example of the French market in 2014, the most represented classes were vaccines (35%), monoclonal antibodies (17%), growth factors (9%), hormones (9%) and enzyme (8%) (14). Biologics can also be segmented according to the therapeutic category: infectiology, oncology, rheumatology, etc. The most represented classes in the French market in 2014 were oncology (17%), infectiology (30%), hemostasis (14%), diabetology (5%) and rheumatology (7%). Regarding the sales, the most sold products are the following: anti TNF, insulin and antineoplastic (see figure 1).

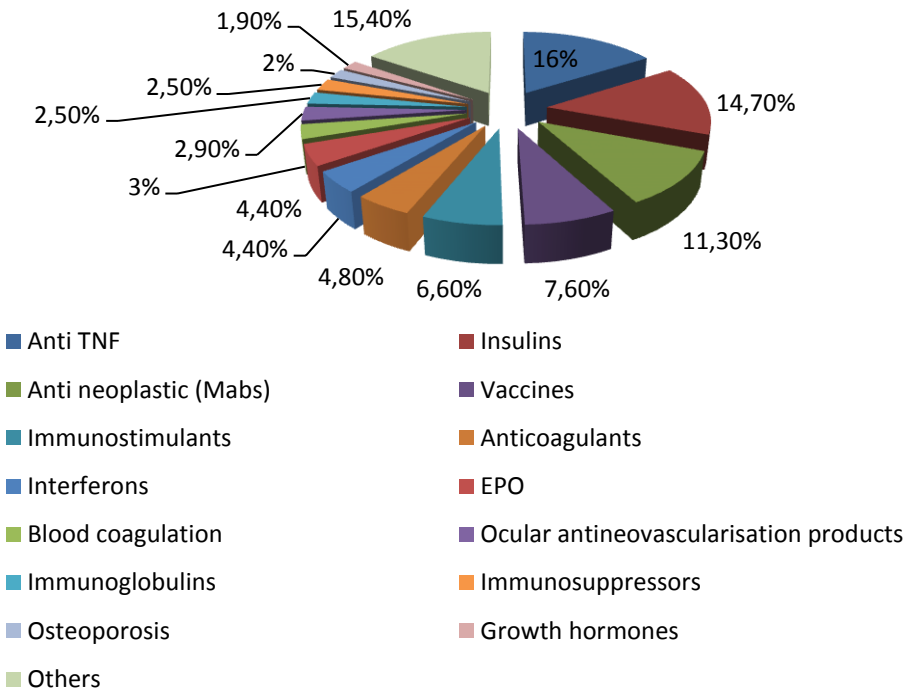


Figure 1 : Top Biologic therapy area, Global sales (Q2 2014) (15)

According to the report of PhRMA concerning the biologics medicines in development in 2013, most of the drugs under development is intended to treat cancers or infectious diseases (16). As the development of pharmaceutical product is a lengthy process, it can be considered that these considerations are still reflective of the current pipelines and that cancer and infectious disease

are still the two major fields in development. Most of these new molecules are monoclonal antibodies or vaccines.

IV.1.c. Characterization

IV.a) Structure

Many biologics are proteins: that means large molecules which properties depend on their tridimensional structure. Part of the constraints related to the formulation of biologics can be explained by their complex structure characterized by different levels of organization (see figure 2). The primary level of protein structure corresponds to the sequence of amino acids residues (it can be composed of 50 to 2000 amino acids residues). The secondary protein structure corresponds to the three-dimensional form of protein defined by the hydrogen bonds formed between amine hydrogen and carbonyl oxygen atoms (α helix and β sheet). The tertiary protein structure is characterized by the geometric shape of the protein. This structure is called the native state of the protein contrary to the denatured state of a protein which corresponds to the unfolded protein. The quaternary protein structure corresponds to the arrangement of multiple folded protein subunits in a multi-subunit complex. Because of this complex structure and the high molecular weight of biopharmaceuticals, delivery of biologics creates challenges.

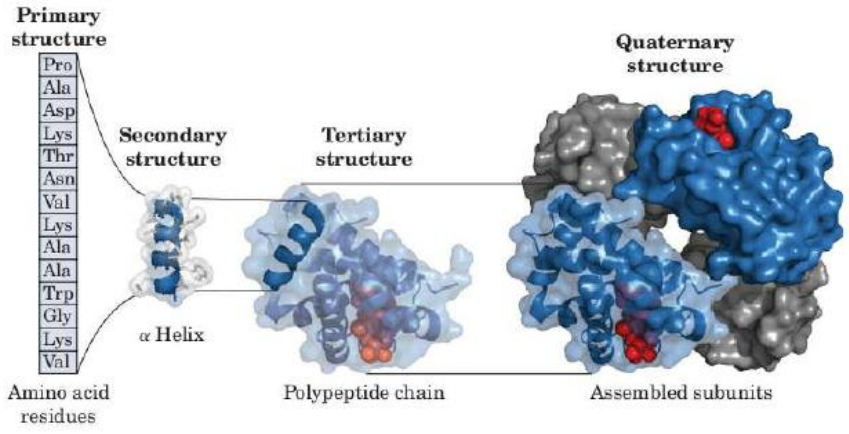


Figure 2: Protein structure (17)

IV.b) Complexity of the manufacturing process

As they have a complex structure, biologics can only be produced using biological expression systems. The manufacturing of many proteins is based on DNA recombinant technology. The process consists in DNA sequences used in the construction of recombinant DNA molecules: the

gene of interest coding for the protein that the pharmaceutical laboratory wants to produce is isolated and inserted in a vector in order to produce an expressed vector. The vector is then introduced into the organism which will express the protein of interest. The protein can be either produced with a unicellular system (such as bacteria, yeast, mammalian cells, insect) or a multicellular system (transgenic plant or animal). The cells are placed into culture; first in a master cell bank and then, in a working cell banks. At this stage, the cell in culture can produce the protein of interest. To produce biologics on a large-scale, cells are cultured into large fermenters. Each step requires quality control to make sure that the protein produced adopts the appropriate configuration. The proteins produced are then isolated from the culture medium through purification. The last step corresponds either to the sterile filtration or to the aseptic filling. (18)

IV.1.d. History

In the late 1790s, the British rural doctor Edward Jenner, noted that the female farmers responsible for milking cows, and who were in daily contact with the cows's virus, never contracted this disease. This cow's virus is called "Vaccine", derived from the Latin word "vacca" for "cow". Based on this observation in 1776, he demonstrated that if we introduce the pus of the "vaccine" by scarification into the human body, it protects against variola. Jenner set out the principle of germs mitigation during the transition between species.

In 1881, the French scientist Louis Pasteur stated the vaccination principle: "weakened viruses having the character to never kill, to give a mild illness which preserves from the fatal disease". Therefore, he began his research on the human vaccination and in 1885, he created the first rabies vaccine and he administered it to Joseph Meister, a nine-year-old child severely bitten by a rabid dog. This vaccine saved his life.

Thanks to a better understanding of the immune system and its implication on the destruction of foreign antigens or bacteria, a new application of immunity is set up. This is called the serum therapy (19). This technique was first developed to treat diphtheria which was a serious illness before the 20^{th} century. It has been showed by Emil von Behring, a Prussian scientist, that when a small dose of toxin isolated from the diphtheria bacterium was injected into animals, the serum extracted from the animal was able to provide immunity to people inoculated with the serum (20). The first successful therapeutic serum treatment of a child suffering from diphtheria occurred in

1891 (20). However, the serum used for serum therapy raised different issues: foreign protein from heterologous sources were immunogenous and could lead to a disease which was called " the serum thickness". Different process were developed by Behring to reduce the side effect of the preparation including serum purification. However, it wasn't a success (21).

The emergence of fundamental breaktrough technologies including restriction enzyme, protein engineering, polymerase chain reaction etc., have contributed to design a new way to produce antibodies. The first technique developed to produce monoclonal antibodies was called the hybridoma technique. It consisted in immunizing species against an antigenic determinant. Then B-lyomphocytes from the spleen expressing antibodies against this specific antigen, are fused with an immortal myeloma cell line. These cells are cultured in a specific medium in order to generate the specific antibody (21) (22). Later transfectomas and chimeric antibodies, humanization technology were developed. The improved knowledge about vectorology has enabled the development of the DNA recombinant technology.

With the emergence of the biologic business, many startup companies have emerged. At the beginning (in the 80s), they were mainly companies based in San Francisco Bay area such as Cetus, Genentech or Amgen. Then, others companies were founded in Europe (Chiron, Biogen, Celltech, etc.) (21). Driven by the challenges faced by pharmaceutical companies that is to say building of new pipeline, optimization of patents, intense competition, intellectual property, there have been many changes in the biotechnology field. Through mergers & acquisitions and licensing, big pharma significantly invested into development and commercialization of biologics. The partnership between pharma and biotech companies, contribute to expand pharma pipelines and drive the biotechnology growth. These partnerships are also an opportunities for biotech making use of Big Pharma' sales forces to achieve better annual sales.

IV.2. Delivery systems

IV.2.a. What is the ideal delivery system for a biologics?

This is an interesting question asked to delivery device experts during interview (see in appendix project leader's interview and device safety leader's interview). The answers were obviously that the ideal way to deliver a drug is the oral administration. However, biologics can't be administered orally.

Indeed, delivering biologics orally represents a unique set of challenges: biologics are degraded by digestive protease and are much larger than traditional small molecules (23). As small molecules and biologics have different properties, their pharmacokinetics also differ (24). Biologics have features which lead to a low oral bioavailability (around 1% (25)). This is mainly caused by their sensitivity to digestive enzyme and pH, their high MW, their poor membrane permeation (26) and their degradation in the gastro intestinal tract. Therefore most of biologics have to be administered through parenteral injection. Intravenous (IV), intramuscular (IM) and subcutaneous (SC) route of administration are the most common ways of delivering biopharmaceuticals (24) (26). Intramuscular injections are commonly used for vaccines whereas intravenous and SC deliveries are generally used for biopharmaceutical drugs such as monoclonal antibodies (26).

Therefore, the question should have been: what is the ideal delivery device for a biologics? The ideal delivery device must obviously meet end user expectations, commercial expectations, technical expectations as well as regulatory expectations. The delivery method should create a positive user experience, which means that patients and caregivers should be willing to reuse it. This is particularly important for chronic conditions in order to ensure patient adherence and compliance. The devices should not constitute an obstacle to the administration. Moreover, the device should be functional and reliable. That means delivering the expected dose in the targeted tissue.

Ideally, the administration should not require any training or should be intuitive and learnable. Indeed, this is a very important point that has been raised during the interview with medical device experts. Syringes and devices should be compatible with self-administration in order to facilitate home care and contain cost. It must ensure usability of the device: it should maximize ease of use, minimize pain and anxiety linked to the administration, and avoid use-related risks.

In the business point of view, the delivery system should sustain competitive advantage to pharmaceutical companies. The devices should be available. It should meet pharmaceutical companies and end users expectations and be offered at the right price. To meet commercial requirements, the devices should obviously be acceptable for the end user. It should work properly and suit delivery requirements.

During the selection of a container for a biologics administered during chronic diseases, different elements have to be considered:

- The medical conditions are important to consider as some patients can have debilitating chronic diseases affecting their ability to carry properly the device. If the chosen device is not appropriate, it can influence the acceptance of the patient. Therefore, the choice of the device must be made accordingly. Moreover, the devices should ensure a minimum of flexibility. The delivery of biologics must be compatible with the lifestyle of chronic disease patients. It is not the case for many traditional self-administered injectables which require to be prepared and delivered at home (vials and single syringes) (27). Ideally the delivery of the biologics has to be easy enough to facilitate the administration. Moreover, it shouldn't require any training. The treatment itself will influence the choice of the device. It will depend on the dose volume, the viscosity but also others features that have an impact on the injection such as light sensitivity.

- The human factor engineering: the factors related to safety and effectiveness must be evaluated in order to determine if end users can use properly the device. Human factors studies aim to ensure the safety and effectiveness of device use. These studies explore the interaction between the people and the container. They make sure that the device is compatible with the human use. The main goals are to improve this compatibility and avoid use error by implementing an appropriate mitigation strategy (28). Therefore the ergonomics should be explored. As patients can have dexterity issues due to their disease (Parkinson, polyarthritis, etc), ergonomic considerations are essential to ensure the delivery of the drug (27), minimize patient anxiety & pain (finer needles, etc.). A lack of considerations of this feature could lead to low adhesion rate by the patient. Low compliance can result from different elements such as frequent dosing requirement, tolerability concerns and so on.

- The primary drug pack must ensure drug/container compatibility and container/device compatibility. The drug/container compatibility is particularly important for biologics which are sensitive and made of complex molecules. As the device safety leader explained during his interview, the stability and compatibility should be ensured during the entire life of the product. The device must ensure the dose accuracy as well as the safety during the administration (such as sterility for parenteral injections).

- The marketing: the devices offered by the competitors are identified to determine if the solution selected is differentiated and can offer a competitive advantage.

- The commercial and operational aspects: a commercial agreement on the device must be reached. A device safety leader also highlighted the time to market as an important element to be considered when choosing a container. Indeed, sometimes pharmaceutical companies preferred to choose a standard container in order to launch their product within the relevant time frame. Others elements are also explored such as the total cost of ownership, the manufacturability, the dual sourcing.

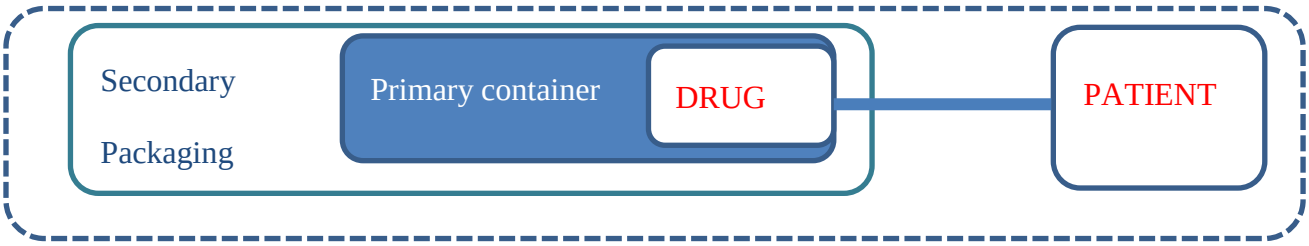
- The technical status: the evidence that proves that the device suits all the requirements must be assessed.

- The regulatory aspects: the regulatory framework of the device must be considered including the combination products rules.

IV.2.b. What are the containers used for biologics?

Packaging may be referred to as primary or secondary. The primary packaging is used to store, transport and administer the drug to patients. To address these properties, this requires the packaging to protect the product against external environment to ensure the stability of the medication. The secondary packagings are pen, autoinjector or safety device that facilitate the administration of the drug. The primary and secondary packaging are a key interface to patient (see figure 3). The choice of the device represents the opportunity to gain patient preference (29).

Figure 3: Drug delivery Device System



Delivery devices companies have developed biotech portfolio to address incompatibility issues between drug and container. These incompatibilities are the result of the high sensitivity of biologics. Syringes specifically designed to mitigate the risk of undesired interactions are offered to biopharmaceutical companies. These suppliers operate in a business to business (B2B) market. That means that the customers of these companies are biopharmaceutical companies which fill the syringes/vials provided by their suppliers with biologics. The delivery device has an impact

on the user compliance but also on the differentiation of the product. There is a broad spectrum of devices used to deliver biologics (see table 2 and 3):

Table 2: Primary containers used for biologics

Containers	Product Description
Vials & Syringe	Biologics can be delivered in multi-dose vials or single dose vials. Multi-dose vials are glass vials used for liquid solution (DTP vaccine) or lyophilized preparation (BCG vaccine). Different sizes are available including 2 doses, 6 doses, 10 doses etc. Generally, multi-dose vial are sold at a lower per dose price. However, this delivery device can lead to safety risk, especially higher risk of contamination, but also higher rate of waste. Moreover, there are many steps to follow leading to potential errors. Single dose vials improves the safety compared to multi-dose presentations, it can be used for more expensive drugs.
Prefilled syringes	Glass pre-filled syringes (PFS), made of type I borosilicate glass, are an increasingly popular form of drug delivery for biologics (30). This trend related to increased demand for prefilled syringe has been confirmed during the interview with a drug delivery expert. It can be either luer based syringes (for IV) or staked needle (for SC and IM). They can be used naked or equipped with a safety device or an autoinjector. To be noticed that plastic PFS are also available in the market but represent a low market share of the PFS market (except in Japan).

Table 3: Delivery Devices used for biologics

Devices	Product description
Safety Syringes	Safety devices are used to prevent safety concerns such as needle-stick injuries caused by recapping contaminated needles. Because it can lead to transmission of pathogens, it is an important concern for healthcare workers. This is mandatory to equip staked needle PFS in many countries.
Autoinjectors & Pen	These devices are used to simplify self-administration of biologics in home settings. They are designed to support the administration of the drug by improving the safety: the delivery device reduces the risk of needle-stick injuries, reducing the anxiety linked to needle and improve the ergonomics of the device. Therefore, the injection is facilitated. Moreover the injection itself is controlled by the device and doesn't require too much injection forces for the patient. Autoinjectors allow the delivery of a fixed single dose whereas pens contain a cartridge allowing multiple variable doses.
Wearable devices	These devices have been designed to address major challenges in the field of drug delivery: deliver high volume of biologics or viscous drugs (Project leader's interview in appendix).

Part of these devices can be used in combination in order to support self-administration of the drugs (see table 4).

Table 4: Self injection devices

Containers	Drug Delivery Systems
Syringe and Vials	Pumps
PFS	Safety systems, autoinjectors
Cartridges	Pen injectors, wearable injectors, pumps
Others	Needle free injectors

IV.2.c. What are the challenges related to parenteral formulations?

Pharmaceutical companies have developed complex parenteral formulation aiming to stabilize the products, to maintain the physical-chemical properties and the structure during the manufacturing, storage and administration. Indeed, the compatibility and the stability are two major concerns for pharmaceutical companies as the device safety leader said during his interview. Different excipients have been developed to stabilize biologics in parenteral solution. However, formulation remains complex for biologics.

IV.a) Challenges related to formulation

There are two majors degradation pathway s of protein:

-The physical degradation is the main cause of degradation and can lead to the aggregation of the protein. This process is mainly influenced by the salt content, pH, ligands and co-solvents. The aggregation can have a clinical impact as it can increase the immunogenicity, the toxicity and reduce the efficacy of the biologics. (31)

-The chemical degradation through hydrolyze and deamination is influenced by pH, salt content, temperature, oxidation (such as hydrogen peroxide, UV, dimethylsulfoxyde) (31).The structure of the protein can be modified leading to a loss of activity and an increase of immunogenicity (31) (32).

All the reactions such as aggregation, deamidation, denaturation and oxidation can have a negative impact on the structure of the protein and can lead to the degradation the molecule (32). In order to ensure consistency in medicine quality, different factors need to be explored during

the development of new formulation such as environmental factors (pH, temperature, salt content, light, but also mechanical shaking, shear stress, freezing, etc).

Different excipients are currently used to stabilize the proteins (see table 5):

Table 5: Excipients used in parenteral formulations

Excipients	Examples
Buffers	Citrate buffer, phosphate buffer
Amino Acids	Histidine, Glycine, Arginine
Carbohydrates	Sucrose, Mannitol
Proteins and polymers	PEG
Salts	NaCl
Surfactants	Polysorbate 20, Polysorbate 80
Antioxidants and chelating agents	EDTA, DTPA
Preservative	Benzyl alcohol
Specific ligands	Metals, Amino acids or Polyanions

(1) Buffers

Buffers are used to stabilize the protein in a targeted pH value which is specific to each protein (33). The pH of the buffer can destabilize the structure of the protein for example the interferon or modify the solubility; it is for example the case of the citrate buffer used in a formulation of high concentration of monoclonal antibodies (34). The choice of the buffer mainly depends on the pKa of the protein as the efficacy of the protein will be optimal when pH = pKa (33). Other elements must be taken into account such as the compatibility between the buffer and the protein.

Certain buffer can be degraded during the conservation leading to destabilization of the protein. Others can cause irritation on the injection site such as the citrate buffer (35).

Changes of temperatures can also have an impact on the buffer. Therefore, additional elements must be carefully assessed particularly during the freeze drying process. For example, the sodium phosphate buffer could crystallize during the freezing leading to important variation of pH.

(2) Amino Acids

Amino acids are used as buffers, stabilizers or antioxidants (31). Histidine, glycine and arginine are the more common amino acids used for the formulation of biologics. Histidine is for example used as a buffer to maintain the pH between 5 to 6,5 (33) but also as a stabilizer for monoclonal antibodies (34) or as antioxidants which trap free radicals (31). Histidine is found in the formulation of therapeutic protein such as Xolair®.

Glycine is used as a buffer but also as blowing agent during the freeze drying process (31) for preparations like Neumega®.

Arginine is used to reduce aggregation, increase the solubility and reduce the viscosity of protein (31). Arginine is also used for the liquid formulation of Avonex® or Enbrel®.

(3) Carbohydrates

Carbohydrates are used to improve the stability of the protein in liquid formulation or lyophilized preparation. They include sucrose, trehalose, sorbitol, mannitol, glucose or lactose (34).

Concerning liquid formulation, carbohydrates are responsible for preferential hydration which improves the stabilization of the protein (34). In the case of solid preparation, carbohydrates are responsible for a vitreous matrix that reduces the molecular mobility and therefore the reactivity.

Mannitol is currently used as bulking agents in lyophilized formulation. By crystallizing out of the amorphous phase of the protein, mannitol provides stability to the protein. It can also be used as a cryoprotectant agent. Sucrose and sorbitol are preferentially used for liquid preparation as mannitol crystallizes at low temperatures (35).

The carbohydrates concentration must be controlled as those molecules can be degraded or contain impurities. Sucrose for example can be hydrolyzed resulting in formation of glucose and fructose which can lead to protein glycation (34).

(4) Proteins and polymers

Hydrophilic polymer such as PEG, polysaccharides (dextrane) or inert proteins (albumin) are used to stabilize protein and improve protein shell (31).

The mechanism is based on the excluded volume. Therefore, stabilization is increased depending on the size of the polymer (31).

Protein excipients such as human serum albumin stabilize protein though competitive adsorption which avoid aggregation caused by adsorption on surfaces (31). This excipient is well tolerated and abundant (36).

(5) Salts

Salts are often added to parenteral solutions to increase the ionic strength which is involved in the protein solubility, physical stability and isotonicity (33). By protecting the protein from repulsive electrostatic interactions, salts stabilize the protein native structure.

Electrolytes can also prevent from attractive electrostatic interactions between proteins which typically lead to protein aggregation in the formulation (35).

They have shown to reduce the viscosity in monoclonal antibodies formulations (33).

It has to be noted that salts can decrease the vitreous transition temperature resulting in difficulties during the freeze drying (34).

(6) Surfactants

Surfactants are used to prevent the aggregation of protein caused by agitation (34). The mechanism of action of those molecules is based on their amphiphilic properties: the molecule move in between the protein and the hydrophobic area (such as air-water interface). The hydrophobic part stay in the interface and the hydrophilic part is oriented towards the solvent (33). Surfactants also reduce the hydrophobic interactions which lead to protein adsorption (36) and a decrease in available protein (36).

Fatty acid ester such as polysorbate 20 and 80 (included in Avonex® or Neupogen® formulations) are the most common surfactants used. However, the action of the surfactants depends on the protein; polysorbates have shown to enhance the stability of certain proteins while reducing the stability of others (33). Moreover, they can lead to the oxidation of certain amino acid residues (34) that's why surfactants need to be used with a concentration as low as possible (31).

(7) Antioxidants and chelating agents

Protein oxidation can be caused by different sources. Metal ions found in pharmaceutical excipients can catalyze oxidation of amino acid residues (34). These oxidations have different

impact: it enhances the protein aggregation; it increases the sensitivity to proteolysis; it decreases the therapeutic activity and it increases the immunogenicity (31). This is a current degradation pathway during the storage (34).

There are a lot of antioxidants such as ascorbic acid or glutathione available in the market but they can destabilize the protein in the presence of metal ions.

Chelating agents such as EDTA or DTPA have shown their ability to avoid oxidation in monoclonal antibodies or human growth factor preparations. Another way to prevent the formulation against the oxidation is to protect the preparation against the light and optimize the pH using amino acids such as methionine or histidine.

(8) Preservative

Preservative are particularly used for multi-dose presentations to prevent the microbial growth. On the contrary, the use of preservative is avoided in single-dose presentation as they can lead to aggregation; it is for example the case with benzyl alcohol (31).

Most of the therapeutic proteins are formulated to be conserved in a single dose container. However, in some cases, when it is possible the development of multi-dose presentation is interesting as it offers more convenience and comfort for patient; it was for example the case with the human growth hormone and multi-dose pen (33).

Pain can be caused by formulation with preservatives. This must be taken into account during the development of a biologics. Phenol and benzyl alcohol seems to induce less pain during the injection compared to m-cresol. Moreover, benzyl alcohol has shown anesthetic properties (33).

(9) Specific ligands

The native conformation of the protein can be ensured by using the natural attachment site. Ligands can be metals, amino acids or polyanions (34). Vaccine, for example, can be stabilized with magnesium (34).

The impact of excipients on the proteins depends on the interactions of the protein with the excipients but also the interaction with the solvent, the container and all the interfaces. (31)

IV.b) Challenges related to container

The main challenge for primary containers is to ensure the compatibility and the stability of the products. A device safety leader insisted particularly on this element during his interview. There is an increasing interest in pre-filled syringes (PFS) for the development of biologics in biopharmaceutical companies. Several biotech products such as ENBREL®, EPOGEN®, ARANESP®, HUMIRA® are available in PFS. Glass prefillable syringes are made of type I borosilicate glass. Plastic syringes made of COP (cyclic olefin polymer) or COC (cyclic olefin copolymer) are also available in the market, particularly in Japan where this technology is currently used. However, plastic syringes still represent an exception and glass barrels are the most common material used in the biopharmaceutical industry.

Different issues of incompatibility can be raised by the use of glass PFS during the development of biologics. Unexpected interactions can be caused by the surface contact between the protein and the container (37). The main concerns are related to tungsten, silicone, leachable and extractible, glue curing:

- The glass barrel is formed and bored with a heated tungsten pin in order to place the needle after. During this step, tungsten oxide can be formed leading to creation of tungsten polyanions (paratungstenate-A or paratungstenate-B) which have been found to interact with some protein (37).

- The silicone is a PFS lubricant used to ensure the syringeability of the device. Silicone can be emulsified into the solution during the filling, generating subvisible particles (SbVPs) in a PFS. These particles can interact with biologics and promote aggregation or co-aggregation of biopharmaceuticals. Some research explores the implication of these aggregate on unwanted immune responses. They are suspected to generate anti-drug antibodies (ADAs). These antibodies neutralize the therapeutic protein and increase their rates of clearance. (38)

V. Results

V.1. Delivery of biologics: Current market

V.1.a. General overview

The drug delivery of biologics is dominated by the parenteral administration. According to a project leader' and a device safety leader's interview, one important new trend in the delivery of biologics is the use of prefilled syringes. These containers are ready-to-use syringes which can be equipped with autoinjector or safety devices. Prefillable syringe offers different benefits compared with vials and syringes. These benefits are applicable both for PFS designed for biologics but also other PFS (vaccines, etc.). As they are ready to use and compatible with self-administration, prefillable syringes respond to the development of home care.

Within the market of containers, prefillable syringes represent a growing market with more than 500 M syringes sold each year for biologics. This is mainly due to the increasing number of biologics under development and launched in the market. As shown in the following figure (see figure 4), there are more and more Investigational New Drug (IND) applications in USA. The IND application aims to ensure that research subjects will not be subject to unreasonable risk before the beginning of clinical trial. If the application is validated by the FDA, the pharmaceutical companies are allowed to start phase I clinical trial for their drug candidates.

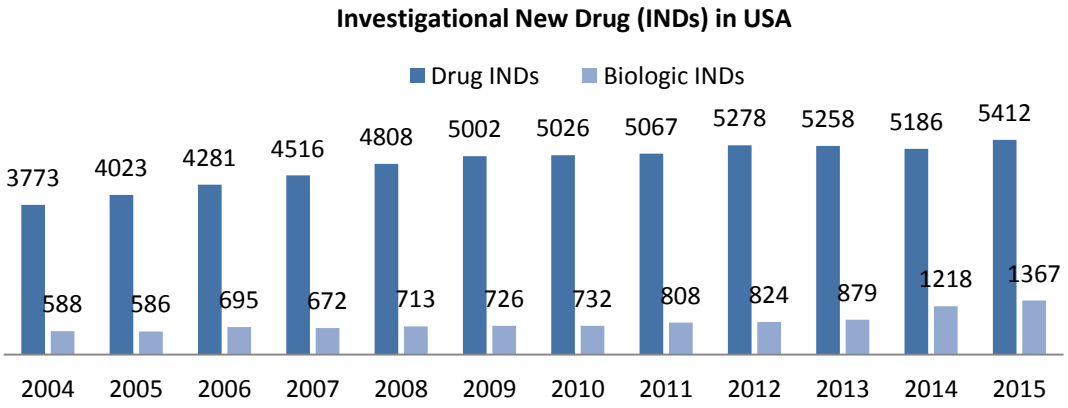


Figure 4: Investigational New Drug (INDs) in USA (39)

To be noticed that the biologics are also expected to be part of the top selling drugs. According to Evaluate Pharma, the compound annual growth rate (CAGR) 2015-2020 is expected to reach 8.7% (see figure 5).

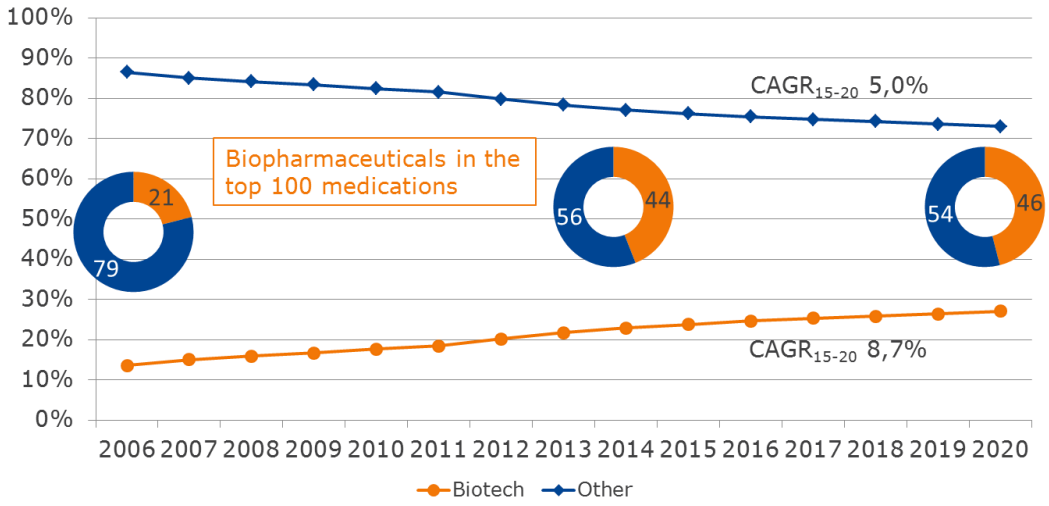


Figure 5: Evolution of the biotech market (39)

V.1.b. Major players

Different players evolve in the delivery systems market for biologics. This includes Becton Dickinson, Ompi, Gerresheimer, SCHOTT. The market of primary container is mainly dominated by Becton Dickinson.

Becton, Dickinson and Company, headquartered in Franklin Lakes, New Jersey, is the leader in the biotech PFS market. This global medical company develops, manufactures and sells a range of medical devices. The company operates through two business segments: BD Medical and BD Life Sciences. Within BD Medical, BD Medical-Pharmaceutical Systems (BDM-PS) develops and designs biologic delivery devices that will be filled with drugs by pharmaceuticals companies. Their portfolio for biologics drugs is mainly based on their new syringe Neopak™ (40) which is their top of the line glass prefillable syringe system. However, other products are offered to customers such as Hypak™ for biotech, safety devices and autoinjectors.

Ompi is a Pharmaceutical Systems division of the Stevanato Group, an Italian multinational company headquartered in Piombino Dese. The company operates through two business segments:

- Pharmaceutical System (which includes Ompi) develops and manufactures glass primary packaging such as ampoules, vials, cartridges and syringes. Their portfolio dedicated to sensitive drugs/biologics is called Ompi Nexa (41).
- Engineering system is specialized in glass forming, inspection system and packaging machines for pharmaceutical industry.

Gerresheimer, headquartered in Dusseldorf, Germany, manufactures specialty glass and plastic products and operates through three business divisions:

- Plastics & Devices: It includes Medical systems whose products are dedicated to the administration of medicines such as insulin pens, inhalers or prefillable syringes. This segment includes the syringe systems which provide PFS for biologics called Gx RTF® to pharmaceutical companies.
- Primary Packaging Glass manufactures and sells glass primary packaging such as vials, cartridge, and jars intended to be used by the pharmaceutical industry, the cosmetic industry and the food and beverage industry.
- Life Science Research manufactures laboratory glassware such as Erlenmeyer, culture tubes or chromatography vials.

SCHOTT Pharmaceutical Packaging, headquartered in Mainz, Germany, is a worldwide supplier of special glass tubing, primary packaging made of glass and polymer, as well as analytical laboratory services for the pharmaceutical industry. SyriQ™ are their prefillable syringes specifically designed for biologics.

V.1.c. Current offer

There are different PFS designed for biologics on the market from different delivery device suppliers. However, these syringes offer very similar value propositions: increased compatibility between drug and container, improved autoinjector compatibility, reduced total cost of ownership.

Therefore, the major differences lie in the services offered by each supplier such as the support regarding the product development and life cycle management, the choice of the device, the regulatory support, the time to market, the risk mitigation and so on. The container offer is summarized in the following table (see table 6). It includes BD Neopak™, OmpiNexa®, Gx RTF® SCHOTT syriQ™. Different volumes and needles are available.

Table 6: Glass PFS for biotech on the market

Companies	Products	Volume	Needle	Needle Shield
Becton Dickinson	Neopak™, Hypak™ for Biotech	1mL- 2.25mL	Staked needle	RNS, NS
			LuerLock	
Ompi	Ompi Nexa®	1mL- 2.25mL	Staked needle	RNS, NS
			LuerLock	
Gerresheimer	Gx RTF®	0.5mL- 1mL 1mL long 1.5- 2.25 mL	Staked needle	FNS, RNS, TERNS
		1mL – 1mL long 1.5mL- 2.25mL- 3mL	LuerLock	n/a
		0.5mL- 1mL 1mL long 1.5mL, 2.25mL, 3mL	Luer Cone	n/a
Schott	SCHOTT syriQ™	0.5 mL, 1mL short, 1 mL long, 2.25 mL	Staked needle	FNS, RNS
		1mL long, 3mL	Luer Lock	n/a
		1mL long, 1mL short 1.25mL,2.25mL, 3mL	Luer Cone	n/a

V.2. What are the current and future boundaries of the delivery of biologics?

PFS offer different advantages. First, the PFS are accurate and safe. Indeed, the devices contribute to reduce medical dosing errors as the syringe is already prefilled with the drug (see project leader's interview in appendix A). (30) Therefore, fewer manipulations are required before the injection; leading to reduced risk of microbial contamination and medication errors (30). This is both useful for patients and nurses.

Second, PFS are cost saving. No medical staff is required as the biologics can be administrated through self-administration. It reduces therapy and injection cost.

Third, PFS are convenient and easy of use for patients and caregivers particularly when combined with an autoinjector.

To conclude, from an industrial point of view, PFS contribute to reduce the "dead volume" and overfilling and thus reduce the total cost of ownership (TCO). This is particularly important for biologics as they are expensive drugs.

However, there are boundaries in the field of drug delivery systems. Parenteral injections have several obvious self-evident limitations such as problem of compliance due to injection constraints for patients: time for them to learn, pain, limitation of the autonomy, etc. The frequency of administration doesn't allow an optimal patient acceptance. Moreover, parenteral route of administration are invasive and can be associated with needle stick injuries, local reaction at the site of injection, etc. Delivery devices are not fully compatible with the fast pace of life as they don't provide flexibility to the patient.

Moreover, the new trends in the field of drug delivery device can raise different concerns. Indeed, as a project leader said during his interview, there is a new trend that consists in reducing the injection frequency. To do so, pharmaceutical companies increase the payload of the drug. However, there is a relationship between viscosity of the formulation and concentration of biologics. Formulations may have higher viscosity which leads to constraints for the design of containers, particularly regarding the injection forces and the secondary container, such as autoinjectors, which have to sustain higher injection forces. Moreover, the relation between pain

and viscosity of formulation is not well defined and could raise concerns regarding the acceptance.

The different factors related to the delivery device market can be summarized in the following SWOT analysis (see table 7).

Table 7: SWOT analysis of the current delivery device market

Strengths	Weaknesses
Gold standard for the delivery of biologics Cost effective Several suppliers Well-established market Low drug waste	Invasive administration which can lead to low compliance/adherence Complicated combination products development Limited options for the formulation
Opportunities	**Threats**
Development of long-acting drugs Growing biologic market	Oral alternatives of biologics (small molecules) Oral delivery of biologics or other routes of administration

V.3. What are the main drivers of the drug delivery systems?

Different factors have been identified as key drivers to encourage pharmaceutical companies to develop new formulations of biologics such as oral administration of biologics. These factors are the following: the patent expiration, the competitive pressure, the growing public health spending, the increasing prevalence of chronic disease and the healthcare landscape. The different drivers have a significant impact on the current trend in the pharmaceutical industry especially on the delivery of biologics. The following part will describe how the market is influenced by these drivers and the trends we have seen developing in the market.

V.3.a. SLEPT analysis

SLEPT analysis (social, legal, economic, political and technological) is a tool commonly used to describe the macro-environmental factors to be taken into consideration during a market research. This allows determine the impact of these factors on our market (see table 8).

Table 8: SLEPT analysis

Socio-cultural	Impact on the delivery device market
Population growth Aging population Obesity & Chronic diseases	Delivery device market is likely to grow due to aging population
Legislation	
Increasing regulatory and legislative restrictions Human factors requirements	Enhancement of quality requirements
Economic	
Global economic crisis Increasing pressure on pricing	Reluctance of customers to spend on healthcare
Political	
Growing political pressure on Healthcare Global governments looking for healthcare savings Promotion of new health behavior/prevention campaign	Drive toward self-administration to contain cost by promoting home care settings
Technological	
Customized treatments	Challenge to create the appropriate offer/services

V.3.b. Patent expiration

Patents provide market protection offering a period of limited competition and monopoly. Consequently, companies can cover investment and generate profit during this period. When the patent expires, lower price version can be introduced by competitors on the market, resulting in a loss of revenue and profitability.

Generic products are allowed to enter the market only after the regulatory approval and the patent expiry. The patent expiries of biologics open the way to develop biosimilars which have a different regulatory status from generics. According to European Medicine Agency (EMA), a biosimilar is: “biological medicine that is similar to another biological medicine that has already

been authorized for use… They can consist of relatively small molecules such as human insulin, erythropoietin, or complex molecules such as monoclonal antibodies" (42).

The patent expiry leads to loss of revenue which forces pharmaceutical companies to look for new revenue streams through lifecycle management. To be noticed that the impact on sales is more limited for biologics compared with chemical drugs as biosimilars may not be automatically substitutable. Different strategies have been developed to sustain competitive advantage when a patent expire also known as pre-expiration strategy (43).

In the pharmaceutical industry, three strategies can be distinguished (see table 9):

Table 9 : Pre expiration Strategies in the Pharmaceutical Industries (43)

Strategy	Explanations
Pre-emptive Launch of Generic	Launching a generic before patent expiration to lengthen the period of attractive profitability
Layering Innovations	Extending exclusivity by adding protected periods
Line Extensions	Altering the chemical composition to create a patentable version of product with an expiring patent

First of all, the company can launch a generic before its drug's patent expires (pre-emptive launch of generic). This aims to optimize the profit capturing share of established markets. To be noticed that the brand name companies have the unique ability to market a generic before the patent expires. They can also give permission to a preferred generic company to manufacture the approved generic. Moreover, this strategy avoids quality concerns for patients that can be raised with other generics as the brand name company manufactures both the brand name product and the generic (43) (44).

Second, the loss of revenue caused by the patent expiry drives the pharmaceutical market. Because of the increased costs associated with discovery and development of a new drug, pharmaceutical companies are highly interested in maximization of existing drugs patents. To do so, the strategy consists of implanting new patent in order to improve the first product aiming to obtain additional period of marketing exclusivity (layering innovations). Different innovations

can be implemented including route of administration, delivery methods, condition of use, dosage form, etc. However, new clinical studies need to be performed to allow the approval of these innovations by the FDA (43) (44).

Third, pharmaceutical companies can also extend the indications for use of the brand name drug by finding new ways to use it (line extensions). This strategy aims to switch current users to a new version of the drug before the generic introduction (43) (44).

The second strategy, namely the layering innovation strategy, is particularly interesting for delivery device companies that can promote delivery systems to help pharmaceutical companies extend their market exclusivity. It also encourages pharmaceutical companies to look after new delivery systems (formulations, dosage, etc.) including oral biologics in order to extend the life of their product.

V.3.c. Competitive pressure

To address the challenge related to competition, biopharmaceutical companies increasingly develop partnership with pharmaceutical companies to reduce the risk associated with the development of their drugs (45). Partnership between device suppliers and pharmaceutical companies is also current. Indeed, because of the combination products rules, the container is now part of the product. Therefore, it's important to consider the delivery method earlier during the development.

Biopharmaceutical companies are more and more interested in devices that bring value to the patient in order to gain patient preference. This is mainly caused by the competitive pressure within the pharmaceutical industry. As a consequence, pharmaceutical companies have to meet end user need in order to keep their competitive advantage. This can be achieved through differentiation by delivery devices, namely diversification of device. This is also true for biologics and biosimilars as biosimilars are allowed to be contained in alternative drug delivery devices. The differentiation aims to meet user requirements. This can also be achieved looking for new routes of administration such as oral biologics.

V.3.d. Public health spending

Health spending grows significantly in Europe. As shown in the figure 6, the healthcare expenditure has increased significantly over the previous five years.

The growing health spending can be explained by different elements. First of all, the aging population grows. In average, seniors need more care, undergo more tests, and receive more prescriptions. They are seen by their general practitioner more often. They are more likely to be hospitalized for long stays and consume more drugs. Therefore, the growing-aged-population is expected to have a significant impact on the healthcare spending.

Second, the increasing prices in the medical field have also an impact on the healthcare spending. Technological progress is very important in this field. The innovation can be the result of quality improvements and new treatments made possible mostly with costly innovations in medical procedures, medical products and medicines.

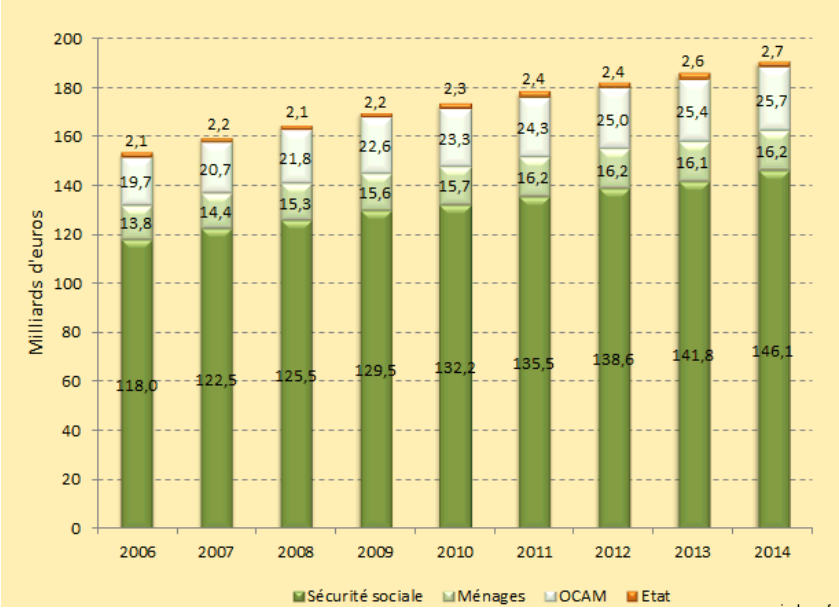


Figure 6: Evolution of Healthcare expenditure in France (46)

In order to prevent too much raise in expenditures, health authorities have promoted new health behavior with prevention campaign. They also have encouraged general practitioners to prescribe generics through control prescription. They have implemented price cuts.

Pharmaceutical companies are encouraged to develop cost effective product for example by reducing the cost associated with the need of caregivers. This also could be achieved promoting oral administration of biologics. This growing health spending has also contributed to drive toward self-administration to contain cost by promoting home care settings and improve convenience. Therefore, the subcutaneous delivery has emerged as a frequently used route making injection easily accessible by patient and accommodating regular regimens. Moreover,

due to home use, heightened safety demands use has led to more sophisticated device: they are designed to avoid needle-stick injuries thanks to needle retraction; they require less education as they are simpler to use; they are essentially safer devices (single use, disposable, shielding).

V.3.e. Chronic diseases

Chronic diseases are a challenge for public health authority as it represents a growing expenditure (47) (48). Moreover, chronic diseases are the main cause of disability and death in the USA (48). The number of patients with a chronic health condition is rising.

Because of the socioeconomic development, a transition from high to low mortality and fertility is occurring (see figure 7). The longer life due to the increased life expectancy is expected to lead to a new disease patterns also known as an "epidemiologic transition" (50). Chronic and degenerative diseases are expected to significantly increase while acute and infectious disease will decrease.

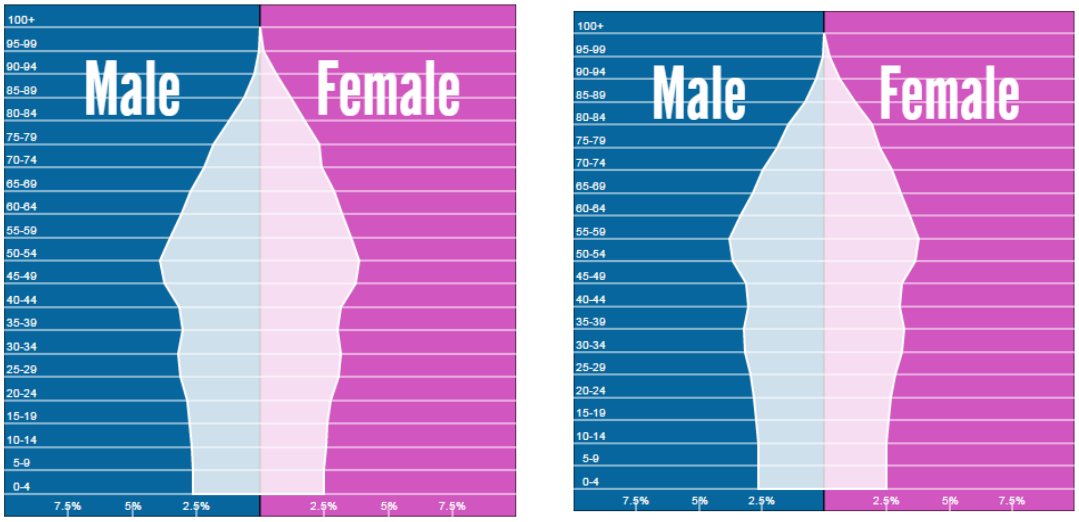


Figure 7: Population Pyramid in Western Europe in 2016 and 2021 (49)

The risk of chronic diseases is also increased by the current lifestyles (tobacco and alcohol use, physical inactivity, poor nutrition, and obesity) which enhance the prevalence of obesity, a risk factor for other chronic diseases such as diabetes or cancers.

Chronic disease represents the majority of the overall healthcare expenditures. According to the national council on aging (NCOA), they represent 75% of healthcare expenditures (51). Therefore, public authorities try increasingly to mitigate the cost associated with chronic diseases

by promoting heath, but also by reducing the hospital care. As previously mentioned, home care settings are a new way to reduce the cost associated with these chronic conditions. Public authorities try to develop patient-centered policies for health promotion developing primary and secondary prevention campaign, treatment and care of chronic diseases (47).

As biologics are mostly used to treat chronic diseases such as diabetes, polyarthritis and autoimmune diseases, the comfort of end user and the compliance are key factors. However, as previously discussed, biologics cannot be delivered orally and must be administered through parenteral route. This results in administration constraints for the patients. As pharmaceutical companies are highly interested by these diseases as it represents a growing market, a new trend emerged: reduce injection frequency in order to increase patient safety & comfort, compliance & adherence and to differentiate. This is also a trend that a project leader explained during his interview. This trend meets both the need of optimizing patent of biologics and reducing the frequency of administration to improve the treatment regimen of chronic diseases.

V.3.f. Healthcare landscape

Biologics like other medications are prescribed by doctors either in the hospital or in medical office. Therefore, the market is driven by the medical community who plays the role of intermediaries. The end user in this field is the patient or the care giver who administrate the drug in some cases. In the healthcare system, regulatory authorities play also a major role as they provide the approval for a new drug to reach the market. The major elements considered by these authorities are the risk/benefit balance. FDA's Center for Drug Evaluation and Research (CDER) ensures that drugs can be used safely by the patients: they evaluate the evidence proving that the drug is safe and effective (52).

The regulatory framework had a significant impact on the delivery device market. In accordance with combination product regulations, drugs have to be developed in parallel to the administration device that will deliver the drug. Combination products are defined by the FDA in 21 CFR 3.2(e) as “a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity” (53). This means that the syringe is now part of the product. Syringe attributes must be evaluated to ensure that the drug will not interact in any unexpected ways with the container (38). Indeed, different issues of

incompatibility can be raised during the development of biologics in PFS (see container part). Unexpected interactions can be caused by the surface contact between the protein and the container because of the silicone or other components, for example. Consequently, pharmaceutical companies have to select the appropriate package to ensure the quality, safety and effectiveness of the combination product.

Human factor considerations are also increasing. Indeed, FDA has increased scrutiny of the human factor section of device submissions. Human factor studies evaluate the interactions between the device and the end user. The main goal is to minimize the use related hazards and demonstrate that the device can be used safely and effectively (54).

To conclude, the regulatory framework is highly demanding with the container requirements. This could have an impact on the market in terms of willingness to find alternative solutions to deliver biologics.

The drivers previously described contribute to modify the current delivery device landscape with the emergence of new trends. It includes differentiation by delivery devices, self-administration, and reduced injection frequency. These trends will be further described in the following part.

V.4. What are the key trends in the field of biologics delivery?

Managing chronic health conditions often requires repeated injection of biologics. As biologics are more and more used to treat chronic conditions, all the elements that could have an impact on the patient's adherence must be considered (for example, the ease of administration, convenience or pain) during the development of new biologics. Therefore, biopharmaceutical companies are currently investing new formulations and delivery methods that could enhance the outcome of chronic treatments. There are different technologies that have emerged in order to obtain long acting formulations. The major ones will be further described below.

V.4.a. Protein modifications

The product improvement through enhancement of the formulation provides an efficient life-cycle management for pharmaceutical companies. There are different technologies which have emerged in the market to improve parenteral biologics delivery. The objectives were to enhance the convenience of administration, the tolerability and the compliance by reducing the injection frequency. These new approaches have been mainly developed to provide long acting protein

formulations. It includes post translational modifications or depot sustained release formulation (55).

V.a) Post-translational modifications

One way to increase the stability and the half-life of the molecule is to graft polymer entities to the proteins leading to a reduced renal clearance via glomerular filtration (26). PEG is the first chemical component explored to be covalently coupled to a protein (26) (55) (56). Besides, there are different pegylated products currently on the market (see table 10).

Table 10: Example of pegylated products on the market (55)

Products	Molecules	Indications
PEGasys®	IFN α- 2a	Hepatitis C
NEULASTA®	G CSF	Chemotherapy induced neutropenia
SOMAVERT®	Growth hormone antagonist	Acromegaly
MACUGEN®	Anti VEGF aptamer	Age related macular degeneration
MIRCERA®	EPO α	Anaemia associated with chronic renal failure
CIMZIA®	Anti TNF α Fab fragment	Crohn's disease

Pegylation offers different advantages:

- It increases the molecular weight of the drug leading to a reduced renal filtration (26) (37). 20 kDa appears to be the minimal molecular weight to efficiently reduce the renal clearance (37);
- It increases the circulating half-life (26) (37);
- It contributes to reducing the immunological recognition, thus protein immunogenicity (26) (37);
- The steric hindrance reduces the enzymatic activity.

However, pegylation has also shown major limitations. The costs of production of biologics are high. Therefore, the pegylation process needs to be highly efficient to optimize the cost of goods. This is particularly challenging as the specificity and the appropriate purity need to be achieved. This means that significant development costs are required to ensure acceptable quality (37). Moreover, pegylated proteins can raise other concerns. Indeed, PEG is not fully biodegradable

by the body. There are not normal detoxification processes that ensure the catabolism of the molecule. This means that they accumulate in the lysosomes potentially leading to lysosomal storage disease. They also generate free radicals which can negatively impact the structure of the therapeutic protein. Alternatives have been explored to meet these challenges. Polysialic acid (PSA) appears as a good alternative for post translational modification of proteins. Indeed, PSA is a biodegradable polymer, non-immunogenic with a long circulatory half-life (37). The production of protein combined with PSA seems to be more reproducible with less polydispersity than PEG products.

V.b) Protein fusion

Recent researches in the field of protein engineering have investigated another approach which consists in a recombinant process that combines the gene of the therapeutic protein with another component such as peptide, antibody fragment (heavy chain of immunoglobulin; Fc fragment). This technology is also known as protein fusion and aims to obtain chimeric protein with longer circulating half-life (26)(55). This approach offers different advantages compared to pegylation: the purification process is simplified and the costs of goods are reduced. The homogeneity of the final product is ensured and there is no extra step during the production that means more competitive production cost. There are already few protein fusions available on the market (see table 11).

Table 11 : Example of Fc fusion proteins on the market (55)

Products	Molecules	Indications
ENBREL®	Etanacerpt	Autoimmune diseases
ORENCIA®	Abatacept	Rheumatoid arthritis
ARCALYST®	Rilonacept	Cryopyrin-associated periodic syndrome
AMEVIVE®	Alefacept	Psoriasis
EYELEA®	Aflibercept	Age related macular degeneration

To summarize, protein modification offers a well-established approach to develop long lasting protein formulation. However, protein fusion and pegylated protein are new molecular entities that require complete clinical trials to be approved. To avoid these constraints, there are other

approaches that have been considered and do not require any modification of the active substance: the sustained release formulations.

V.4.b. Sustained-release formulations

Another approach that doesn't require chemical modification of the protein has been developed and consists in sustained release formulation of the drug. This allows the development of formulation of drug already on the market as life-cycle management strategy. It includes different technologies summarized in the table 12:

Table 12: Delivery technologies for parenteral administration

Method	Advantages	Limitations
Microparticles	- Control the release of the molecule - Compatible with subcutaneous injection	- Adverse events related to burst release - Large scale manufacturing is difficult and the production costs are high
Nanoparticles	- Better permeation	- Non specific uptake
Depot injections	- Different dosage forms	- Larger gauge needle/ incisions for surgical implants

Microparticles are used to increase the half-life of the proteins, peptides or small molecules (26) (55) (57). The drug is encapsulated with a biocompatible polymer, such as polylactic co glycolic acid (PLGA). This polymer is already used in the market for the formulation of peptide (26) (55). These systems provide a protection to the drug and allow obtaining the release of the protein at a controlled rate (57). Different factors influence the release of the drug: the fabrication method (57), the molecular mass of the polymer and the protein which will influence the diffusion of the protein across the microparticle (26), the properties of the polymer (size of the particles, copolymer, shape and porosity) (57), excipients added to stabilize the protein, etc. However, encapsulation can raise different issues during the process. The drug release is difficult to control (57). Moreover, the protein can be aggregated or denatured leading to an inactivation of the protein. To prevent those reactions and enhance the stabilization of the structure of the protein, excipients can be added.

Nanoparticles are designed to deliver smaller molecules. The main advantage of such delivery method is a better permeation into tumors. There are different applications in early stage of development for example cytokines for tumor immunotherapy (26). This technology can be combined with a pegylation process in order to enhance the circulation of nanoparticles and optimize tissue permeation.

Depot injections are an alternative to particulate formulation. It includes different technologies: reverse thermal gelling systems, biodegradable polymer or lipid depots for subcutaneous delivery solid implants, etc. There are already commercial products of depot injection, for example, goserelin acetate, an LRH agonist.

V.4.c. Delivery devices

In parallel to long lasting formulations, the development of innovative devices emerged in the market. It includes needle free devices, an approach of injection without needle. However, needle free injectors don't address the injection issues as they are associated with low acceptance. Indeed, they can cause pain and bruising at the site of injection. Moreover, the amount of drug that is delivered is variable (26). Therefore, they are not broadly applicable for protein delivery.

V.4.d. Alternative routes of administration

Alternatives routes of administration have been developed to offer less invasive route compared to parenteral administration. Potential advantages of these alternatives include a reduced need for vigilance unlike injections which raise sterility and stability concerns. This might lead to lower costs, wider accessibility, better outcomes and reduced biohazardous waste and risk of infection, etc. (58) Therefore, other routes of administration have been explored in order to improve the convenience and the compliance of patients. It includes nasal, pulmonary, oral, transdermal, vaginal, etc.

The alternative routes include:

- Pulmonary route, which is characterized by a large surface area available for drug absorption with thin alveolar epithelium allowing a rapid absorption of the drug and a good vascularization. These features mean that lungs can allow systemic delivery (59). However different barriers remain and can slow down the absorption of the drug (pulmonary enzymes, macrophages, mucociliary clearance, respiratory mucus, etc.) (59).

In addition, the duration of action and the ease of use of the product are still challenges that need to be overcome. The delivery of protein through pulmonary route have already been achieved and marketed in 2006. Indeed, inhaled insulin has been approved by FDA, but the drug was discontinued in 2007 due to associated high costs and a low penetration in the market (26).

- Transdermal administration corresponds either to the formulation or to devices placed in the skin which will allow the delivery of the active substance across the skin without pain. However, this application is limited to low molecular mass hydrophobic molecules (26).
- Oral administration is considered as the more convenient route to deliver a drug. There are a lot of startups which currently work on oral delivery mechanism for biologics (4). The challenges related to oral administration will be further discussed in the following part.

V.5. Oral delivery: a new perspective for biologics?

Oral delivery is generally considered as the optimal route of administration for drugs (see project leader's interview and device safety leader's interview in appendix A and B). It offers more convenience and less invasive routes for patients. We will further explore this route of administration as it seems to be the Holy Grail for pharmaceutical companies.

V.5.a. What advantages could provide oral administration?

The oral route of administration offers different advantages that interviewed people also highlighted:

For end users: oral administration should facilitate the therapeutic regimens of the drug and improve the patient acceptance. It also reduces the risk of contamination. It is more flexible compared to injections which can require preparation (60).

For pharmaceutical companies: oral administration should help them to gain patient preference. It is also a way of differentiation. They also can increase life cycle of current drug through an oral formulation of their marketed drugs.

For healthcare systems: This route doesn't require medical staff, so it is more affordable. Oral delivery doesn't lead to biohazardous waste. Therefore, it could reduce the management of these

wastes which are potential threats to public health or the environment. Oral formulations also avoid the problem of cold chain management (See in appendix A).

V.5.b. Which challenges need to be overcome to deliver oral protein?

The properties of biologics have raised many challenges in the field of drug delivery systems and formulation. These challenges will be further described in this part.

V.a) Absorption mechanisms

The major site of absorption in the gastrointestinal tract is the small intestine (about 90% of all nutrients). The small intestine has three distinct regions: the duodenum, jejunum, and ileum. The mucosa of the small intestine is characterized by *plicae circulares* intestinal, *villi* and *microvilli*, which increase the amount of surface area available for the absorption. Each *villus* has a network of capillaries and lymphatic vessels called lacteals close to its surface. There are two pathways for molecules to be absorbed in the small intestine via lymphatic vessels or via venous vessels. Understanding the underlying mechanisms which modulate the lymphatic absorption is particularly interesting as this pathway avoid the hepatic first pass metabolism. Therefore, enhancing the absorption into the lymph could improve the bioavailability of the drug (61).

To be noticed that there has been also an increasing interest in targeting colonic delivery because of the 20-60 times lower proteolysis activity compared with the intestine. However, there are different barriers: the individual variation of colonic bacteria, the higher residence time which higher expose to colonic proteolysis. Therefore, we will focus our research on mechanism related to delivery on the small intestine (see figure 8).

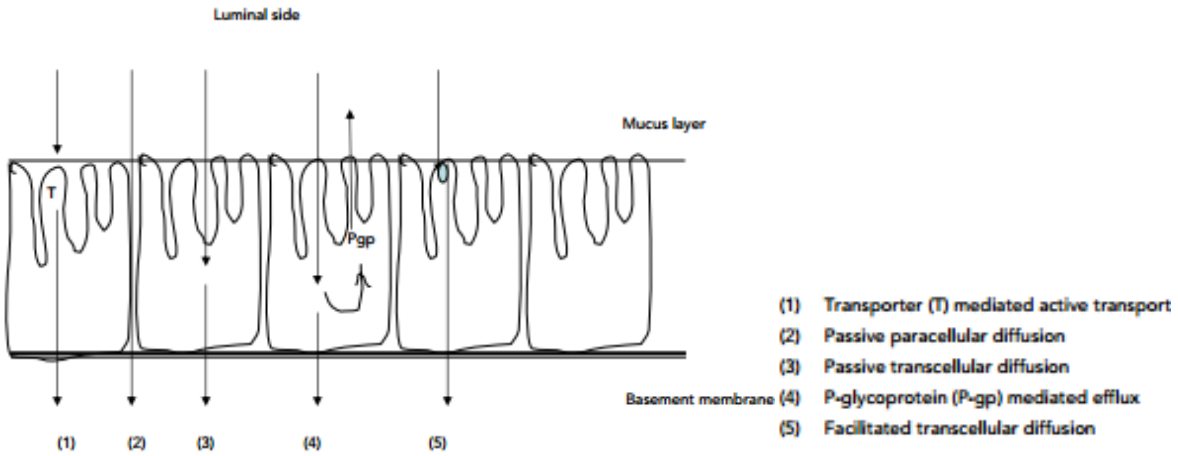


Figure 8: Routes of drug transport across cell barrier (61)

There are different mechanisms involved in the crossing of a drug from the intestinal lumen to blood flow. This includes simple diffusion, that means: paracellular or transcellular transport; pinocytosis, active transport or carrier mediated transport (60) (61). To cross the intestinal barrier, a biologic has to use one of these transports. In the case of biologics, the passive diffusion is the major transport mechanism. It can be either paracellular or transcellular diffusion (61). The paracellular diffusion is the diffusion through the lipophilic tight junctions whereas transcellular diffusion is the diffusion through the lipophilic absorptive cells. To determine which way will use a protein to cross the intestine wall, the hydrophobicity of the molecule have to be considered. Hydrophilic molecules are more likely to follow the paracellular diffusion whereas hydrophobic molecules are more likely to follow transcellular diffusion (61).

The passive diffusion mainly depends on the characteristics of the drug such as physicochemical properties and diffusive properties of the molecule. The degree of absorption of the proteins will lie on the hydrophilic-lipophilic balance of the molecule (HLB), on its charge and on its size (61).

V.a) Barriers to oral absorption

Biological activity of biologics is based on their complex structure. If the structure is altered by degradation or denaturation, this will lead to a loss of activity. The delivery system has to ensure the stability of the molecule. This is particularly challenging for oral administration as the molecules may come into contact with enzymes, drastic pH and various chemical environments. In this part, the different barriers to the delivery of oral biologics will be explored.

The following table (see table 13) highlights the main elements that influence the pharmacokinetics of biologics.

Table 13 : Key Factors in Determining the ADME Properties of Biologics (24)

ADME: absorption, distribution, metabolism, and excretion – MW / molecular weight – GI: gastrointestinal – FcRn: neonatal Fc receptor – ICs: immune complexes – RES: reticuloendothelial system

ADME related considerations	Key determination factors
Physicochemical properties	Large MW and size, hydrophilicity, shape, charge, limited solubility, GI degradation, stability, heterogeneity in isoforms
Absorption mechanisms	Route of administration, convective transport through lymphatic vessels, diffusion across blood vessels, dose, injection site and volume, species differences, subject characteristics, presystemic metabolism/catabolism, FcRn –and target– dependent mechanisms, physicochemical properties
Distribution patterns	Physicochemical and binding properties, route of administration, production process, FcRn –and target– dependent mechanisms, convective transport, transcytosis, affinity, binding site barrier, inflamed tissues
Metabolic mechanisms	Nonspecific endocytosis, degradation by proteolysis, local metabolism, FcγR- and target-mediated clearance, ICs formation, physicochemical properties
Elimination mechanisms	Metabolism/catabolism, excretion, proteolysis, RES, Fc –receptor and target– mediated clearance, nonspecific endocytosis and ICs formation followed by complement- or Fc receptor mediated clearance, protection from catabolism via Fc mechanism, binding affinities, physicochemical properties

There are different considerations that explain how complex it is to deliver biologics orally. Indeed, there are three main barriers that limit the bioavailability of biologics administered orally: physical barriers, chemical barriers and biochemical barriers.

As shown in the previous table (see table 13), there are different physical barriers that limit the permeation of biologics. Indeed, proteins are hydrophilic molecules (that means with a limited hydrophobicity), with a high molecular weight, poorly soluble in the gastrointestinal fluid, leading to a low permeability (24) (60). Therefore, it's difficult for these molecules to cross

biological membranes. However, pharmaceutical companies can modulate some of these parameters to improve the permeability. This is the case, for example, for the charge of the molecule or its solubility which can be enhanced through the formulation or chemical adjustments. For example, the pegylation contributes to increase the solubility of the molecules (61).

There is also the chemical barrier that represents a challenge to deliver biologics orally due to the protein degradation by the acid environment.

The last barrier is the biochemical barrier. Proteins and peptides are physiologically degraded by digestive enzymes into amino acids or shorter peptides in order to be absorbed. There are three major enzymes: trypsin, chymotrypsin and pepsin, involved in the degradation of proteins in the gastro intestinal tract (62). The small intestine is a site where the amount of peptidase is critical. These enzymes are secreted from the mucosa but also from the pancreas. The brush border membrane is also a major enzymatic barrier which contributes to the low bioavailability of proteins (61).

V.5.c. How to overcome these challenges?

To be orally administrated, proteins should be protected against the gastric acids and the action of enzymes that degrades the protein in the stomach and in the bowels. The biologics should also be solubilized and cross the basement membrane of the bowel to reach the bloodstream or the lymph (25). Different technologies are used to overcome these challenges (see figure 9). This includes:

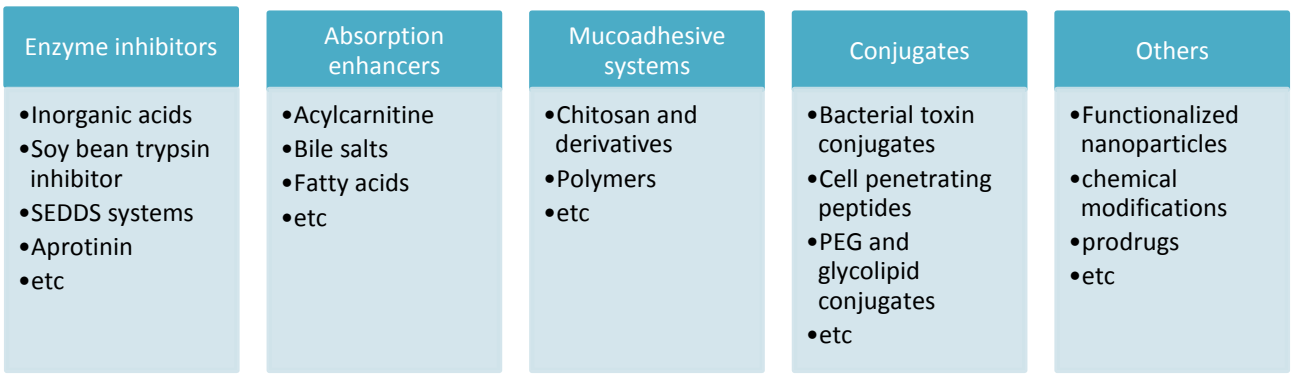


Figure 9: Technological approaches (63)

Some technologies can be combined in order to achieve better bioavailability. This is the case for permeation enhancers and protease inhibitors.

V.a) Enzyme inhibitors

There are around 40 different peptidases in the GI tract. One way to increase the oral bioavailability is to add enzymatic inhibitors such as protease inhibitors to inhibit the enzymes that degrade protein in the gastro-intestinal tract leading to an increased absorption (23) (64). Aprotinin is widely used (trypsin/chymotrypsin inhibitor) (61)(64)(65), but other enzyme inhibitors have been developed: soybean trypsin inhibitors, camostat mesilate and chromostatin (65). The choice of the inhibitors will mainly depend on the structure of the biologics. However, these inhibitors are not specific and can affect the degradation of other proteins and could lead to a reduced digestion of protein. The use of the inhibitors can lead to a deficiency of the enzyme in humans (60). On the contrary, the protein malabsorption could stimulate the peptidase secretion (65). There is another mechanism that can be used to decrease the enzymatic activity. It consists on locally modifying the pH away from the optimum value of the peptidase inhibiting intestinal protease (66).

V.b) Absorption enhancers

Absorption enhancers namely permeation enhancers are used to increase trans-epithelial transport (23). Oral absorption enhancers are excipients that increase the oral absorption and therefore the bioavailability of the protein (65)(67). They promote the crossing of the epithelial membrane. There are different mechanisms of action:

- The molecule can disrupt the lipid bilayer of epithelial cell (surfactants) leading to an increased transcellular permeation (65).
- The molecule can decrease the viscosity of the intestinal mucus to improve the absorption (65).
- The molecule can form complex with calcium or modify the properties of tight junctions and lead to temporary opening of the tight junctions (chelating agents, fatty acids, toxins like Zonula occludens toxin) (60). This reversible opening leads to increased paracellular permeability. (65)

They can be surfactants, chelating agents, bile salts, polymers, fatty acids and their derivatives (67). It has been suggested that carrier molecules such as butyric acid, sodium myristate or

sodium taurodeoxycholate could interact with proteins through non covalent interaction enhancing the drug permeation (61).

However, protease inhibitors and permeation enhancers do not always improve bioavailability, and can present additional safety concerns, especially in the context of a chronic use (23). Indeed, even if the intestinal epithelium is constantly renewing, the epithelium can be damaged leading to a local inflammation of the intestine, intestinal epithelium ulceration, membrane erosion (60) (65). Moreover, the permeation enhancers not just facilitate the crossing of molecules but also the crossing of pathogens which may cause infections (65).Calcium chelators can be responsible for calcium depletion which can have severe consequences (61).

V.c) Mucoadhesive polymers

Mucoadhesive polymers are biocompatible and biodegradable polymers used to adhere to the mucosal epithelial surface and enhance the amount of protein available to the target site by increasing the time available for absorption (60) (61) (64). The therapeutic effect is obtained limiting the side effects. The polymers used include both synthetic bioadhesive polymers such as polyacrylic acid (carbopol, polycarbophil, etc) and cellulose derivatives (carboxymethylcellulose, hydroxypropyl cellulose), and semi natural bio adhesive such as chitosan, xanthan, etc. There are different concerns regarding this approach. Indeed, the mechanism of action is not well understood and they are suspected to modify the tight-junction properties (65).

V.d) Carrier systems

Different carrier systems have been developed to deliver proteins and peptides. It includes emulsion, microspheres, liposomes, nanoparticles, etc. The main objectives of these carriers are to protect the molecules.

- Emulsions produced with lipophilic surfactant are used to protect the protein from the chemical and enzymatic environment in the bowel (25). The main challenge with emulsion is the stability of the formulation (60). Moreover, the absorption may be influenced by the size of the particles and the amount of lipid in the formulation (61).
- Hydrogels have been developed to protect the molecules against the proteolysis and degradation. The pH responsive hydrogel protects the molecules in acid environment while the polymer dissociates in basic or neutral environment.

- The delivery of the active substance can also be controlled using polymers. This sustained-release pharmaceutical preparation allows a reduced frequency of administration (64). Nanoparticles and microparticles have emerged as a major driver in the clinical application of biologics (23). They protect the protein and allow a sustained-release of the drug. These forms can be addressed to a target site reducing potential side effects (64).
- Microspheres are used to protect the protein from the acidity (25).
- Liposomes are composed of a bilayer of phospholipid. They prevent from the degradation of the protein and improve the bioavailability of proteins (64).

V.e) Chemical modification of the proteins

There are different interests in modifying the proteins structure: enhance the penetration of the protein, minimize the immunogenicity and improve the enzymatic stability (61).

There are two ways of modifying a protein:

- A modification of the amino-acids group
- A modification of the carbohydrate part

As an example, the Thyroptropin Releasing Hormone (TRH) is a tripeptide Glu-His-Pro which has a really poor bioavailability. TRH analogs with modification of the proline have been tested. This has led to molecules with lower clearance and higher activity.

Some examples in the literature show that the modifications, which increase the oral bioavailability, can in parallel decrease the biological activity. Moreover, the modification of the structure can have consequences. It has been noticed that the modification affecting the conformation of the protein could have an impact on the activity of the protein.

The advantage of the modification of the carbohydrate part is that the primary structure of the protein remains the same (61).

There is another way to improve the oral absorption of drugs, also known as hydrophobization. This can be achieved either by including more hydrophobic amino acids in the protein or by conjugating the protein with a hydrophobic compound such as a lipid or a polymer (for example palmitoylation of insulin) (66). This approach aims to stabilize the proteins but also to enhance

the diffusion of proteins across the intestine barrier. The literature also suggests that this approach could increase the crossing via carrier-mediated-uptake (61).

Peptides or proteins can also be combined with polyethylene glycol. This approach has already been explored for injectable molecules including SOMAVERT®, MIRCERA®, CIMZIA® and has resulted in less frequent administration requirements. For oral administration, pegylation may have different interests: it can increase the stability of the molecule, it also enhance the resistance to enzymatic digestion (66).

To ensure the biological activity of biologics, other considerations have to be explored during the product development:

- Many proteins have a short half-life mainly due to the degradation of the molecules by enzyme complexes leading to a quick clearance *in vivo* (60).
- A precise dose needs to be delivered in the blood flow to reach the expected activity. Certain biologics can have a narrow therapeutic index (60). Therefore, the variability must be minimal to avoid side effects, but also to ensure the activity *in vivo*.
- Biologics are expensive drugs mainly because of the complex technology used to design these products. That means that pharmaceutical companies must avoid to waste active substance to ensure a sufficient bioavailability.

V.5.d. Marketed products

There are none currently marketed oral protein. However, there are some marketed oral peptides. Most of them are cyclic peptides (63) such as COLOMYCIN® colistin sulfate, NEORAL® cyclosporine, VANCOCIN® vancomycine, etc. Cyclic peptides are more resistant to enzymatic degradation due to their low structure flexibility (66). The following list (see table 14) is not exhaustive but the objectives were to give some examples of the current technological advancement in oral delivery of peptides.

Table 14: Marketed oral peptides (63) (66)

Companies	Products	Peptides	Indication	Delivery	Mw (g/mole)
Biocodon Ltd	KOOLISTIN®	Colistin sulfate	digestive tract infections	Acts locally	1268
Novartis	NEORAL®	Cyclosporine	Immunosuppression	SNEDDS, systemic delivery	1202
ANI Pharmaceuticals	VANCOCIN®	Vancomycin	digestive tract infections	Acts locally	1485
Ironwood Pharma	LINZESS®	Linactotide	Irritable bowel syndrome	Acts locally	1527
Mitsubishi Tanabe Pharma	CEREDIST®	Taltirelin	Spinocerebellar degeneration	Chemical modification, Systemic delivery	477

Most of them act locally in the gastrointestinal tract: COLOMYCIN®, VANCOCIN®, and LINZESS®. However, there are marketed peptides such as CEREDIST® taltirelin, a molecule used to treat spinocerebellar ataxia, which acts centrally. This demonstrates that it's possible to commercially develop a drug managing low and variable bioavailability of the molecule (63).

V.a) Linaclotide

IRONWOOD PHARMACEUTICALS, INC is a biotechnology company that aims to develop and commercialize new medicines. They're particularly evolving in areas of large unmet needs such as irritable bowel syndrome with constipation (IBS-C), chronic idiopathic constipation (CIC) or refractory gastroesophageal reflux disease (GERD) (68).

The only commercial product at the moment is linaclotide. The drug is a guanylate cyclase C agonist. It is a 14 amino acid peptide. The absorption of the peptide is very low. The molecule acts locally on the intestinal epithelium and increases concentrations of cyclic guanosine monophosphate (cGMP). This increase of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen leading to an increased intestinal fluid and accelerated transit (69) (70). The mechanism of action of LINZESS® is to stimulate bowel movements in order to relieve constipation (70). The treatment is indicated in adults for irritable bowel syndrome with constipation or chronic idiopathic constipation. Linaclotide has been approved by

FDA in 2012. The drug is available in the United States under the trademarked name LINZESS®, and is available in certain European countries under the trademarked name CONSTELLA®. LINZESS® is a capsule taken once daily on an empty stomach, at least 30 minutes before the first meal of the day. The formulation consists of microcrystalline cellulose spheres with coatings containing the linaclotide and an outer enteric coating. These beads are loaded into a capsule (66).

Ironwood pharmaceutical plans to develop a second generation of linaclotide in collaboration with Allergan. This new generation aims to improve abdominal pain relief for patients with disorders where lower abdominal pain is a current symptom, such as irritable bowel syndrome with constipation. Even if it's an oral biologics, linaclotide acts locally and doesn't cross the epithelial barrier, which means that it doesn't overcome the current challenges for most of biologics administered parenterally.

V.b) Vancomycin

Vancomycin is an antibiotic firstly administered via parenteral injection. It has been developed and marketed by Eli Lilly to face the increasing resistance against penicillin. The molecule is not well absorbed mainly because of its hydrophobicity and size. The oral formulation of vancomycin is used to treat locally infection in the gastrointestinal tract mainly pseudomembranous colitis (66).

V.c) Cyclosporine A

Novartis has developed SANDIMMUNE®, the first oral cyclosporine A in the market. The cyclic peptide is combined with a non-ionic surfactant that contributes to improve the oral bioavailability. However, high inter-individual and intra individual variability were reported mainly due to metabolism reactions (66). NEORAL®, the next generation of oral cyclosporine, has been developed with a new delivery systems based on a self-nanoemulsifying drug delivery systems (SNEDDS). This improved formulation facilitates the solubilisation of the molecule leading to a better release and a demonstrated enhancement in oral bioavailability.

V.d) Taltirelin

Taltirelin (MW 477g/mole) is an analogue of the TRH (Thyrotropin-Releasing Hormone). This molecule has been designed to have a better stability compared to TRH and a longer half-life.

This oral formulation has been on the Japanese market for decades. A next generation of TRH analogue that aims to treat degenerative conditions is in preclinical development (66).

V.5.e. Oral delivery technologies & clinical applications

As highlighted in the previous part, deliver peptides orally is possible. In this part, the platform and technology that allow the development of biologics; both peptide and protein, are explored. The selected delivery technologies that are described below (see table 15) are either in advanced stage of development or innovative approach (robotic pill).

Table 15: Main technologies developed to deliver proteins and peptides

Company	Technology name	Mechanism of action	Formulation
Merrion pharmaceuticals	GIPET™	Absorption enhancers : medium chain fatty acid	Tablet
Emisphere	Eligen™	Absorption enhancers : SNAC, SNAD, 5-CNAC	Tablet
Chiasma	TPE™	Suspension of peptides in oils and absorption enhancers such as castor oil	Capsule
Proxima	Axcess™	Absorption enhancers : Aromatic alcohols	Capsule
Oramed	POD™	Absorption enhancers and protease inhibitors	Capsule
Enteris Biopharma	Peptilligence™	Absorption enhancers (acylcarnitine) and protease inhibitors (citric acid)	Tablet
Rani therapeutics	Robotic pill	Intestinal injections / microneedle made of sugar and preloaded with peptides	Capsule

V.a) MERRION PHARMACEUTICALS & NOVO NORDISK

MERRION PHARMACEUTICAL had developed oral forms of biologics using its proprietary GIPET® technology (65) (71): **G**astro**I**ntestinal **P**ermeation **E**nhancement **T**echnology. GIPET® is a technology designed to improve the absorption of oral biologics using patented absorption enhancers. The main constituent of this formulation is a medium chain fatty acid: C10. This enhancer activates micelle absorption allowing the transport of the molecule across the epithelium into the blood vessels. With this technology, the bioavailability of biologics is improved (72).

Merrion pharmaceutical partnered with other pharmaceutical companies to deliver biologics. The main partner was Novo Nordisk. The License Agreements between Merrion pharmaceutical &

Novo Nordisk covered the development of oral forms of a number of analogues of insulin and GLP-1, molecules used to treat diabetes. Merrion pharmaceutical decided last year to sell IP Asset to Novo Nordisk in order to pay off a $5 million loan from Irelandia Investments. Therefore, the company received $3 million from Novo Nordisk for the sale of the IP and $10 million in accelerated milestone and royalty payments under the existing licenses related to GIPET between the companies. The licenses will then be terminated (see Novo Nordisk part).

V.b) EMISPHERE TECHNOLOGIES & NOVO NORDISK

EMISPHERE TECHNOLOGIES is a company that aims to develop new oral formulations to replace injectable formulations. To do so, the Eligen® Technology has developed a platform of carriers that enhance the permeability across intestinal epithelium (see patents in appendix). The Eligen® drug delivery technology is used to ensure an effective oral absorption of peptides or biologics products by improving bioavailability, absorption or by decreasing time to onset of action (73).

The main absorption-enhancing carrier molecules used are:

- monosodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC)
- N-[8-(5-chlorosalicyloyl)-amino] caprylic acid5- (CNAC) (60) (73)
- (4-[(4-chloro- 2-hydroxy- benzoyl)amino] butanoic acid (4- CNAB): (65)
- (N-(10-[2-hydroxybenzoyl]-amino) decanoic acid (SNAD) (65)

These molecules are not considered as new chemical entities as the carrier interact with the active substance by non-covalent complexation (60). Therefore, the interaction is reversible and the complex dissociates after having crossed the intestinal barrier. Moreover, unlike some other permeation enhancers, SNAC is claimed to not generate intestinal damage. This is a safe excipient already used in the formulation of nutrients and dietary supplements (65). The drugs used in combination with Eligen® are at an advanced stage of development, or have already received regulatory approval. Their main partner is Novo Nordisk which started Phase IIIa clinical trials for oral semaglutide at the beginning of 2016 (see Novo Nordisk part). Emisphere continue to identify and secure new Eligen® Technology partnerships (73).

V.a) NOVO NORDISK

NOVO NORDISK is a pharmaceutical company headquartered in Bagsvaerd, in Denmark. The company is particularly focused on four therapeutic areas: diabetes, obesity, hemophilia and growth disorders. The main value of Novo Nordisk is to improve health and quality of life for people with diabetes and other serious chronic diseases (74). The goal of the company is to discover, develop and manufacture innovative biologics and make them accessible to patients throughout the world. Their current strategy is to expand their leadership in diabetes (75). As previously discussed, Novo Nordisk is well engaged in the development of oral biologics in the field of diabetes treatment. In August 2015, Novo Nordisk decided to initiate a phase IIIa program with oral semaglutide, a once-daily oral formulation of the long-acting GLP-1 analogue semaglutide based on the Eligen® technology. Indeed, Novo Nordisk announced in February 2015 that they have encouraging results of the proof-of-concept phase II trial. Moreover, Novo Nordisk plans to start a global phase IIIa program, named PIONEER, comprising ten trials (see table 16). These trials include more than 9,000 people with type 2 diabetes. The goal of this program is to demonstrate the safety and efficacy of oral semaglutide, but also to evaluate the cardiovascular safety of oral semaglutide.

Table 16: Novo Nordisk Clinical trials for oral formulation

Clinical trials	Therapeutic area	Description	Phase
OG217SC NN9924	Type 2 diabetes	A long-acting oral GLP-1 analogue intended as a once-daily tablet treatment for people with type 2 diabetes.	III
OI338GT NN1953	Type 1 and 2 diabetes	A long-acting basal insulin analogue intended to offer the clinical benefits of a basal insulin analogue in a once-daily tablet.	IIa
OI320GT NN1957	Type 2 diabetes	A long-acting basal insulin in an oral formulation intended as a once-daily tablet treatment.	I

V.a) CHIASMA

CHIASMA has developed a proprietary Transient Permeability Enhancer (TPE®) (65). This consists in an enteric-coated hydrophilic microparticle that contains the drug, sodium caprylate (60) (65) with castor oil and/or caprylic acid in an emulsion format. This platform aims to facilitate gastrointestinal absorption of drugs into the bloodstream by enhancing the transcellular path permeability. TPE® can deliver macromolecules from 4 to 10 kDa.

Chiasma uses this technology to develop an oral form of Octreotide (conditionally trade named Mycapssa®). Octreotide is a peptide and a somatostatin analog. This molecule is used to treat acromegaly which is a rare disease caused by benign tumor of the pituitary gland. This disease is characterized by an excess release of growth hormone. Octreotide is a peptide which mechanism of action is to mimic the effect of somatostatin, a hormone that reduces the release of growth hormone. Clinical trials have been completed for oral Octreotide.

Phase III trial enrolled 155 people diagnosed with acromegaly and managed on somatostatin analogs. The safety profile of oral octreotide was consistent with the profile of injectable octreotide formulations. However, FDA rejected the new drug application (NDA) for Mycapssa on April 15, 2016. Therefore, an additional international Phase III trial is conducted to support a potential Marketing Authorization Application with the European Medicines Agency and to reassess the U.S. regulatory strategy.

V.b) PROXIMA CONCEPTS'AXCESS

The Axcess oral delivery technology has been developed in order to enhance the bioavailability of peptides. This technology is based on the use of aromatic alcohols as absorption enhancer enteric coatings, additives that modulate intestinal proteolytic activity, and a caprylic acid derivative which facilitates transport across the membrane of the small intestine. This works by improving the permeation across the cell membrane and opening up the tight junctions between intestinal cells (76).

This technology has been used to develop oral calcitonin and PTH products to treat osteoporosis, a degenerative skeletal disease and Paget's disease, an incurable chronic bone disorder. Human phase IIa clinical trials have been completed for insulin and salmon calcitonin as well as a phase I trial for parathyroid hormone. In addition, phase I is in the planning stage for two further molecules of high potential market value.

V.c) ORAMED PHARMACEUTICALS

ORAMED PHARMACEUTICALS (NASDAQ: ORMP) has developed POD™ technology (Protein Oral Delivery), an oral delivery technology to administer insulin and GLP1 orally in order to treat patients with diabetes (77). The technology consists in enteric coated capsules that contain an oily suspension of the drug with permeation enhancers and enzyme inhibitors (65).

V.d) ENTERIS BIOPHARMA

ENTERIS BIOPHARMA, a biotechnology company developing innovative drug products, has developed a cutting edge oral drug delivery technology called Peptelligence™, which is an oral drug delivery platform (65) (78) (79). This technology aims to orally deliver biologics/peptides that have been previously marketed as injectable formulations. The formulation is based on an absorption promoter (see figure 10) (79).

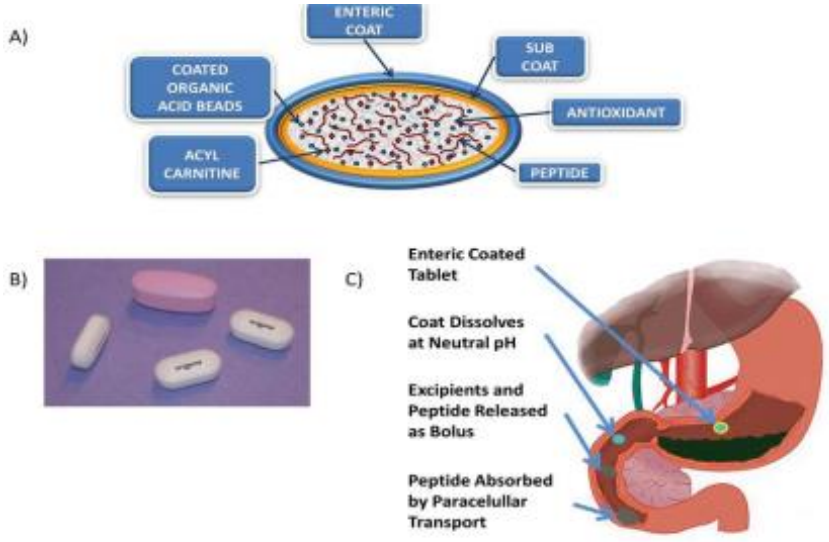


Figure 10: Mechanism of Peptelligence in Enteric-Coated Tablets (78)

As described in the figure above (A), the tablet contains lyophilized peptide, coated citric acid acylcarnitine, an antioxidant, microcrystalline cellulose, a disintegrant, a dry binder, and a lubricant (78).

Microcrystalline cellulose, disintegrant, dry binder, and lubricant are often found in the formulation of tablets. Antioxidant is used, in this case, to prevent oxidation of amino acids. Citric acid acts as a calcium chelator and membrane permeation enhancer. Acylcarnitine is a

surfactant that enhances solubilization but also permeation by loosening tight junctions in the intestinal enterocytes and allowing paracellular transport. It is also claimed to help penetrate intestinal mucus (65)

These excipients are blended and compressed to form a tablet (B). In order to protect peptides from hydrolysis or degradation, the tablet is coated with a water-soluble polymer-based subcoat, followed by an acid-stable enteric-coating. This coating is designed to be dissolved in the duodenum, that means when the pH is above 5.5 (C) (78) (79).

There are currently two drugs that are under development (79):

- Ovarest™ (oral leuprolide tablet) phase I have been developed using Peptelligence™ in order to treat endometriosis with a daily oral treatment of leuprolide. Endometriosis is a painful and chronic disease currently treated with monthly depot injections.
- Tobrate™ (oral tobramycin tablet) have been developed using Peptelligence™ in order to treat uncomplicated urinary tract infections offering an alternative to current treatments that are less effective due to antibiotic resistance.

This technology has been used to develop a peripherally acting kappa opioid receptor agonist currently in development for the treatment of acute and chronic pain and pruritus (80).

The bioavailability using the Peptelligence™ technology mainly depends on the physicochemical properties of the peptide, such as size, charge, stability, and hydrophobicity (65). Therefore, we can conclude that this technology is not appropriate to deliver molecules with higher size than peptides.

V.e) RANI THERAPEUTICS

RANI THERAPEUTICS is a startup that develops novel approaches to deliver large drug molecules orally, which to date can only be delivered through injections. This approach differs from the other as the technology is based on injections in the intestine, taking advantage of the fact that this organ doesn't have sharp pain receptors (see figure 11) (81).

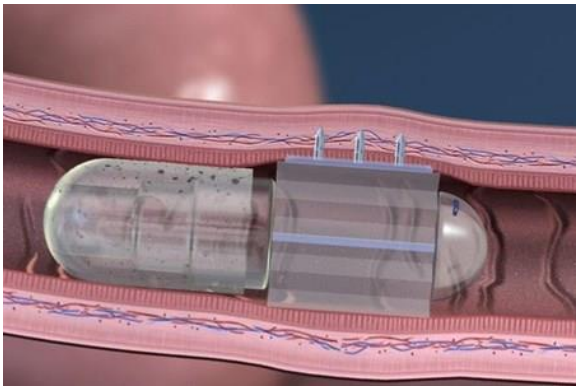


Figure 11: Robotic pill, RANI THERAPEUTICS&NOVARTIS (82)

RANI THERAPEUTICS has developed a robotic pill designed to facilitate the oral administration of biologics. The intact pill travels through the gastro-intestinal tract until it gets to a specific pH in the intestine; a pH sensitive coating dissolve once the pH reaches 6.5 (81) (82). The force required to put the needle into the intestine mucosal wall is developed with a self-inflating balloon. Indeed, when the outer layer of the pill is dissolved, a valve which initially separate citric acid and sodium bicarbonate is exposed (81). The mixes of these two chemicals is responsible for the formation of carbon dioxide which inflates the balloon-like structure. This structure is covered with microneedles that attach the surface of the intestine. These microneedles are made of polysaccharides loaded with the drug. The studies have been set up to determine which kind of molecules can be efficiently administered through the pill (82). It had been shown that molecule could be delivered whatever their molecular weight (hormone, monoclonal antibodies, etc.). The preclinical results are promising with oral bioavailability reaching more than 50 % (65). According to Mir Imran, the reproducibility reached 95% in animals. The main limit of this approach is the payload of the biologics: the upper limit is almost 5mg (see table 17) (81).

Table 17: Pros and Cons of Rani Therapeutics

Pros	Cons
Good bioavailability	No clinical data
Good reproducibility	Limited payload of biologics
Administration of biologics with high molecular weight	Potential side effects of intestinal injections
	Cost of the technology

V.f) Clinical applications

As shown in the table below (see table 18), the development of oral delivery systems mainly concerns the diabetes. This can be explained by the market attractiveness: diabetes is a chronic disease increasingly widespread in the population. The estimated prevalence of the disease was 8.5% in 2014 (83). Moreover, the benefit of oral delivery for this chronic disease is high as patients have to inject themselves several times a day. The oral administration could facilitate the long-term medication for diabetes patients.

Table 18: Clinical applications

Companies	Partnership	Therapeutic area	Molecules	Phase
Merrion	Novo Nordisk	Diabete	Insulin based and GLP1 analogues	IIa
Emisphere Technologies	Novo Nordisk	Diabete	Semaglutide (GLP1 agonist)	IIIa (84)
Diabetology Ltd		Diabete	Oral insulin, PTH, Calcitonin	IIa
Oramed	Novartis		ORMD-0801	II
Oramed	Novartis	Diabete	GLP1 agonist	I
Enteris Biopharma	Tarsa Therapeutics	chronic pain treatment based on a peptide	Calcitonin	III
Chiasma	Roche	Acromegaly	Octreotide	Phase III
Rani Therapeutics and Novartis	Novartis	-	Insulin, monoclonal antibodies	Preclinical

VI. Discussion

This research allows putting in parallel both challenges related to formulation and administration; two fields which should be explored together during the development of a new product or a new formulation. It has been shown that this development is particularly complex for biologics and is evolving with the end user need, but also the changing environment. The evolution of this market has been discussed with delivery device and formulation experts who provide us their market picture. Trends that arise from the drivers of this market have been identified. The major one is the development of long-acting products that aim to reduce the number of injections and enhance the convenience of treatments. Different technologies have been identified including protein engineering (pegylation, fusion proteins, etc.) and sustained-release formulations (micro/nano particles, implants, etc). In parallel to these advancements, new challenges have been raised: the development of alternative routes of administration for biologics.

The research highlights the solutions that aim to improve the bioavailability of oral biological products. Although they are promising, these technologies don't allow the delivery of most of biologics mainly because of their high instability and their large size. Peptides remain the preferred candidates. Two main approaches can be distinguished: robotic pills of Rani therapeutics and other technologies based on the permeation enhancers. The clinical applications show that most of the molecule candidates are peptides (hormone, GLP1) with the exception of robotic pills candidates. Indeed, they seem to be better candidates to be delivered orally. This is probably because of their size which allows a better crossing via transcellular or paracellular diffusion. There is a negative correlation between molecular weight and oral bioavailability: high molecular weight molecule has a lower bioavailability. It can be concluded that molecular weight is still a hurdle for the oral absorption.

Furthermore, even if some of permeation enhancer technology has shown positive results, different safety concerns can be raised: enzyme inhibitors could affect the degradation of other proteins and lead to a reduced digestion of protein; calcium chelators can be responsible for calcium depletion which can have severe consequences; permeation enhancers can be responsible for superficial mucosal injuries that are part of their mechanism of action. The repeated action of these enhancers could have negative impact in the context of a chronic disease with daily administration. Pharmaceutical companies obviously encouraged the use of well-

known enhancers to mitigate the risk of toxicity and of failure. Over the last decades, permeation enhancers have been studied to deliver biologics orally, such as insulin, somatostatin, PTH, etc., For small peptides, there have been some successes. However, these formulations are subject to inter-individual variability due to intestinal transit, dilution in the intestinal fluids, residence time in the intestine, diet, but also due to intra individual variability. This variability is a major barrier for drug with narrow therapeutic index. Therefore, potential candidates for oral administration are preferentially peptides with large therapeutic windows.

Permeation enhancers have been tested for years and haven't modified the landscape of biologics delivery so far. Their main interest remains the delivery of peptides. Therefore, it can be considered that they don't represent a major threat for current delivery market of biologics. It will probably represent a niche market in the future with a limited growth. To quantify this market, the number of peptides under development that are designed to be delivered orally should be determined. This metrics should provide more information about the impact on the delivery device market.

Based on these observations, it can be concluded that robotic pills have more chance to be disruptive in the market as this technology allow the delivery of biologics without any size restriction. Even if we don't have the necessary distance at the moment to judge this technology, it seems that they have attracted big investors such as Google venture and Novartis. That means that preclinical data are robust, interesting and promising: good oral bioavailability and reproducibility. As molecular weight is not a limitation for robotic pills, there are much more potential candidates for robotic pills. However, the technology has never been tested for human use. This is a key milestone to determine if the delivery is effective and safe. The clinical trial success rate for this kind of combination product is not well known. However, it can be guessed that the risk of failure is not negligible. To better identify the targeted market and evaluate the potential impact on the current delivery device and the impact on prefilled syringe market, it could be interesting to quantify the number of biologics into the market that can potentially be loaded in these pills as they can only deliver 3mg to 5mg. Obviously the current payload of these drugs, the half-life and their pharmacokinetic properties should be considered to perform such analysis. However, even if those robotic pills could be applicable for a large amount of molecules, each situation should be considered separately. In terms of regulatory approval, the laboratories should demonstrate its superiority over the current treatments. Compared to a

sustained release formulation of a biologic which can require an injection every 6 months, a daily oral administration is not always relevant.

The transition from invasive procedures to more convenient routes of administration should be considered by pharmaceutical companies. It could provide lots of benefit for these companies: additional patent for commercially successful drugs and extended market exclusivity patents; better compliance which contributes to improve the patient's health. As a result, perception of the drug's efficacy improves, thus boosting the company's reputation.

THÈSE SOUTENUE par Mme PRÉVITALI Pauline

CONCLUSION

The oral route of administration is considered as the ideal route as it's the one which offers the more convenience for patients. However, biologics are not good candidates for this route as they are degraded in the gastrointestinal tract and are poorly absorbed. Therefore, they are administered through parenteral injection. Prefilled syringes are the emerging container used to deliver biologics. Even if they offer lots of benefits, such as delivering the accurate dose and supporting self-administration, injections are still constraining, especially for chronic disease patients treated with biologics.

For decades, pharmaceutical companies have been looking for alternatives that could improve patient acceptance and convenience. Developing alternative administration methods for existing biologics can help these companies extend market exclusivity. Oral administration is one of the explored alternatives. Different challenges need to be overcome to successfully deliver oral biologics. The main hurdles include physical barriers, chemical barriers and biochemical barriers.

Different technologies have been suggested to improve the bioavailability of biological products; for example, permeation enhancers, enzyme inhibitors, carriers, etc. However, despite all the efforts of the research, the results are mixed: there is not a disruptive technology that guarantees the delivery of biologics orally. There is not a successful protein marketed that crosses the intestine barrier to reach the bloodstream. Moreover, it seems that the size of the molecule is a serious limitation for the current delivery methods as most of the candidates are peptides or small proteins. Furthermore, safety concerns related to certain compounds used to enhance the bioavailability are also raised. Robotic pill is a different way of approaching the oral administration and could be disruptive in the market. The first results from clinical trials might give us clues on whether this technology works.

Based on these observations, it can be concluded that the impact of oral route of administration for biologics on the prefilled syringe market is not expected to be significant in the next five years. Even if the current clinical trials for oral insulin are conclusive, the device market that should be the more impacted would be the cartridge and pen in Europe and vials and single syringe in USA. Other routes of administration are considered as a potential alternative of injectable, for example transdermal administration. These approaches should be further explored to determine their role in the future therapeutic arsenal.

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Dijon, le 04 / 11 /2016
Le Vice-Doyen,

Y. ARTUR

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APPENDICES

APPENDIX A: Worldwide project leader's Interview

The interviewee currently works as worldwide project leader at Becton Dickinson. He is responsible for innovation at BD Medical-Pharmaceutical Systems and has a great understanding of medical device market but also of drug delivery challenges within the pharmaceutical industry. During this interview, he was asked to share his knowledge about the new trends and his view on the biologics market.

According to you, what is the ideal drug delivery system for biologics?

The ideal drug delivery for both biological drugs and other medications is the oral route of administration as it is more convenient for patients. Oral route of administration doesn't require a specific technical process unlike injection or auto injection. During the development of a new drug, the oral delivery is always the first to be considered. If it can be done, it's the route preferentially used. If it's impossible because of the formulation or the structure of the molecule (this is the case for most biologics that are not compatible with gastrointestinal tract), the injection is considered; the injection is a second choice.

What are the trends in terms of drug delivery systems on the biologic market?

The current trend is to expand the time between injections (for example by developing long acting drugs), so that patients suffering from chronic disease don't need to inject too often the medication. Typically, in the past, treatments with daily doses were developed; nowadays, pharmaceutical companies try to develop treatment regimen with less frequent injection such as a dose once a week, every 15 days or once a month. For example, copaxone® used to be injected daily, now the medication is administered 3 doses a week.

What is the impact of this trend on the device market?

Unlike diabetes patients who have to inject themselves the drug several times a day, patients requiring less frequents injections will not master the injection procedures rapidly; they may encounter more difficulties to inject themselves the medication. Therefore, they need easy to use devices in order to simplify the injection. The necessary training to learn how to inject properly the drug must be basic as the patient will have to remember it. That really needs to be simple,

intuitive, but also reassuring. The indicators should confirm that the injection was successful, fully made, and that no problems have occurred during the injection.

How do pharmaceutical companies make a choice about the container? Which criteria are considered?

Different factors need to be considered. First of all, the dose of the medication gives us the information about the volume and the frequency of administration; then, physicochemical properties of the molecule/formulation are also explored. If the pharmaceutical company wants to expand the injections by concentrating the solution, this can have an impact on the solution viscosity for example. It can be decided to dilute the solution. In that case, the volume will increase and we can choose high volume injection delivery device such as 2.25 mL PFS or patch injector (for volume above 2/3mL). Patch injectors are devices that are designed to be worn next to the skin. They will continuously delivery the medication (during few minutes or even few hours). Below 2mL, PFS can be used with an auto injector.

Among all containers available, what are the main advantages of PFS?

The main advantage of PFS is that it removes the potential dosing errors. Unlike vials, the prefilled syringe contains the right dose of medication and doesn't require any manipulation or reconstitute of the solutions. Thanks to the PFS, the right dose is delivered at the end of the injection without margin of errors. The other advantage is that PFS is ready for use. As I said, no preparation nor reconstitution are required. If the PFS is equipped with a safety device, it avoids needle stick injuries which are a serious concern especially for medical staff. Compared with naked syringe and vials, PFS doesn't require to change the needle, so it mitigates the risk of contamination and the risk of needle stick injuries.

To summarize, PFS means right dose and ease of use.

Regarding the prices, is it more expensive compared with vials?

The price per dose is more expensive with a PFS. However, in the field of biotech, there are not a lot of vials as auto-injection is very important. Vials are used for administration in hospital. In that case, medical staff is trained to inject.

For biologics, the price of the container is negligible compared to the price of the medication. This is not the case for other markets such as anticoagulant or vaccine.

Which markets are the more interesting for oral biologics?

Oral insulin is the Holy Grail. The number of diabetes patients exploded in emerging countries such as India or China. There are lots of companies who tried to enter this market. Obviously, all the chronic diseases with an important prevalence and which are expected to grow are interesting.

Novo Nordisk has developed oral insulin; if this product is marketed, which market would be the most affected?

For me, if it works, it will not necessarily impact the pump market which provides an optimum convenience. I think that it will mainly target people who use pen and syringes. In the USA, nearly half of the diabetes patients use vials with syringes; pumps are also widespread. In Europe, this is different; the pen is more used, and also a bit the pumps.

APPENDIX B: Device Safety Leader's Interview

The interviewee currently works as Device Safety Leader at Bayer Pharma AG. He is a pharmaceutical packaging and medical device expert with broad experience in all aspects of packaging and medical device development, quality control, data, project management, risk management and device vigilance. During this interview, he was asked to share his knowledge about the new trends and his view on the drug delivery market.

What is the ideal route of administration for a drug?

I think that the ideal route of administration is of course more or less the oral route. However, usually for biologics, it doesn't work so. So we talk about injection for most of the products. Regarding injections, subcutaneous is the preferred one as it's the easiest one from an application perspective and it is something that can also be done by patients even if it has to be done regularly. So it's the preferred way among the existing alternatives. But of course the best way is always the oral way.

For biologics, which criteria are considered when choosing a drug delivery system?

Actually there are two separated topics. So first, if you have a product which does not require additional preparation, if you do not have powder or freeze dried products that need to be reconstituted, what you ideally have is a prefilled syringe. This is always the easiest way, also for the patient.. In some cases, you cannot achieve that for a product because the development timeline for prefilled syringes are much longer than a standard vial and single use syringe. Criteria at the end are to have a convenient and friendly system which can be used without any specific training. I think in general the requirement is to have efficient stability of the drug during storage and transportation. This is not the main topic but, in addition to that, sometimes, you have of course to consider the lead time to bring the drug into the market so you might start with a not ideal version from a user ending perspective, but a version which can get easily into the market; that is also sometimes the criteria. In other cases, you need devices to allow easy reconstitution and it can be more complicated because depending on if it's a one-time task or if you need to do it regularly, you have to consider human interface, a main criteria to allow easy reconstitution without a lot of training and so on. At the end, whenever you have a device, it's all about human factor safety and efficacy of the entire process.

Many biologics are used to treat chronic disease. What trends in terms of delivery devices have emerged within the industry?

Yes, I think one trend is of course to have prefilled syringes. I think not for all products but this is increasing. I think the other trend, if you are talking about injections, is to have injection devices whatever they might be that allow injecting a product ideally without the need to see a needle. It allows smooth injection and it is not too manual I think specially in the case of chronic diseases where the patient has to perform the injection.

What are the main challenges in delivering biologics?

In terms of delivery systems, it's of course the compatibility with the system which means the stability of the drug in the delivery system, how long it is ensured, that is the main point. If you talk about syringes, you have a bit more complex system where you have also different materials; this often leads of course, to more issues compared to standard vials. That needs to be considered as well. I think from an injection perspective, at least to my experience, we do not have issue with viscosity or something like that. That's not the case so far, I think it's really about compatibility. In addition to that, for some drugs, we had the experience, with very small volumes required. This leads to different issues: the dosage accuracy but also the filling accuracy in the manufacturing process. So that means that you don't have to fill too much and you have again the issue that you need to have a strong dosing, function which ensure that you do not overdose on the patient side; so that's also a topic. I think these are the main issues.

What are the main advantages to offer prefilled syringes for chronic diseases?

At the end, it's a convenient route that makes it easier for the patient. It's also a safety advantage because the reconstitution from one container to another container is always a risk. It's the main reason to have it. But also for commercial aspects, from a competition perspective, it's easier I would say to justify your product if you have a prefilled option compared to a non-prefilled option. It represents a greater benefit if the injection is actually not performed by the user himself but for instance by the physician, and also because if you have ready to fill or prefilled syringe you also have the time saving advantaged in the clinics which can justify your product compared to other products.

Regarding safety device and human factor studies, what are the challenges?

I think what we have today in place is a development process that considers the human factor really early on. The biggest challenge is when you have to treat chronic disease patients. They represent a really broad population from young people to old people, maybe people with or without disabilities. You have not a unique user population which from a development perspective makes it difficult because you have to cover all the potential scenarios. So that's the challenge, but at the end due to the device process which is based of course on the design control, this will be considered early on in the development phase and anyway you have to perform a study to validate your device to meet user expectations. I think it's not a big issue from a regulatory perspective. There is not really a need to provide evidence that you considered human factors activities during the development process. But I think that we do that and this design control approach have to you considered all the risk and human factors requirement in your development. Then I would say, from an application perspective, the main issue does not really concern the syringe. The main issue is related to any reconstitution step you might have, but also with the injection at the end.

During the development of a new drug, when do pharmaceutical companies start looking at the device?

That's a good question. I think that the issue is that the tractive element process if you have a new drug is very much focusing on the development of the drug at the end. I think that the issue is that we even might get a lot of information very late in the process. So, you even might not know if it's really liquid at the end or if it's a solid dosage form. You might not have really information on the dosage nor the volume. That might not be clear early on. It might not be clear what the target indications at the end are. For small population, we may not do a syringe development process and all this things. So, this is something which is available very late in the process. And I think often it's so late that if you have all this information in place, if you would then start the syringe development process, you might not complete such project before the actual drug development process. That means that you need to wait for the market launch for development of the syringe. That is something that is not intended usually. So then, what we have is that early on in the process whenever you know what kind of formulation is developed, you use a type of standard packaging system for example a vial with a standard closure. And

later on, as part of the post market sale for the drug, you would start then to develop for instance a syringe or you would start a little bit before the launch with a syringe, but you would not launch the product in a syringe; and later on you would market additional features or additional injection systems or whatever you need. So that means that at the end, you start at a very late phase, most probably during phase III study, with the final development of your closure system and reconstitution device. For the initial market launch, you often use standard containers which are not that convenient for the patients.

For a drug, if you want to change the container, what are the regulatory constraints?

That's an issue of course. I think what you have to demonstrate is the compatibility, if it's safe and appropriate to be used with the drug. That means usually that what you have to do is of course a material qualification. You have to show if it's compatible with the drug, that it's safe for the user, you have to show that you can manufacture the product according to the requirements, which means you have to perform validation, so you have to produce a certain number of batches, for instance three batches of the product. And you have to provide evidence to demonstrate that everything is fine for initial registration, but also for a change. This is a time consuming step.

From a patient point of view, what are the main inconveniences of the current devices?

I think of course, if you have reconstitution, it's always difficult for users as you have a lot of steps to perform. The injection itself of course is one of the issues. It's also how to organize and manage from a patient perspective. If you really have a trained patient, if you do not consider the injection itself, I think the main issue is the reconstitution. With prefillable syringes, that is not so complicated, I would say especially for population who has to inject themselves a medication regularly; they get trained. The main issue is really to perform the injection itself.

Is the device a way for pharmaceutical companies to differentiate and gain patient preference?

I think it's of course a way to demonstrate higher compliance if you have complex injection system. The issue is that on the market if we have a biological product which is pretty old, the competitors have also some delivery systems which are not that good as ours and of course they have a lower price. You will not get more money, you can make your price higher, even though

you have a better system and even though it's demonstrated that it's more convenient for the patient. I think that's an issue on one hand. On the other hand, if it's less convenient you have of course lots of costs related to adverse event report for instance. So it's also beneficial for the company to provide convenient products to the patient. It's of course a main consideration how to make a drug safe and effective and delivery system can help to have a better drug at the end. And if you see that you have a competitor with a similar indication but with a different reconstitution system or different injection system, I think is the benefit of the drug from a medical perspective is more important than the consideration of what might be improved regarding your delivery system. The delivery device is an advantage only if you have similar products as long as your product is not good from an efficacy perspective.

APPENDIX C: Vice president peptides's Interview

The interviewee, PhD in materials science currently works as Vice President, Peptides, in Ipsen. He has focused his research on new formulation and drug delivery technologies, especially for proteins and peptides. In this interview, he will discuss the oral protein and peptide technologies that are in advanced clinical development.

Quelles sont selon vous les technologies les plus avancées et qui ont le plus de chances de succès concernant la délivrance de protéines et de peptides?

Pour le moment, ce sont des produits qui sont en développement. Il n'y a rien sur le marché car c'est un vrai challenge d'administrer des peptides et des protéines par voie orale. Il existe toutefois quelques peptides sur le marché, mais ils ont souvent une action locale dans le tractus gastro-intestinal. Les biomédicaments sont des produits très fragiles qui se dégradent dans l'estomac à pH acide et qui sont détruits par tout un arsenal d'enzymes comme les peptidases... De plus, elles doivent traverser l'épithélium intestinal, soit de nombreuses barrières. C'est pour cela qu'il n'y a pas de protéines à ce jour sur le marché. Pour les peptides, il en existe certains administrés par voie orale, qui ont des effets essentiellement locaux, par exemple le linaclotide Linzess®. Je pense qu'il n'y en a qu'un qui ait un effet vraiment systémique et qui passe la barrière intestinale : le Ceredist® taltirelin, dont la masse moléculaire relativement faible est d'environ 500. Autrement, il existe quelques autres peptides comme la desmopressine. D'autres sont en développement, notamment un analogue de la somatostatine comme l'octreotide, développé par la société CHIASMA pour traiter l'acromégalie qui est en phase III, soit un stade déjà bien avancé. Un dossier a déjà été déposé, mais il a été rejeté par la FDA ; la phase III doit donc être refaite.

Le gros problème, c'est la biodisponibilité de ces produits. Il est nécessaire de délivrer des doses très élevées comparées aux doses sous-cutanées. C'est une difficulté importante. Les autres difficultés sont les interactions avec les autres médicaments, qu'on appelle *drug-drug interactions*, et les effets de la nourriture, c'est-à-dire que si le médicament est administré au moment du repas par exemple, on peut avoir une variabilité assez importante de l'efficacité due à ces effets-là.

J'ai identifié différentes technologies qui permettent la délivrance de peptides par voie oral, tel que peptilligence, GIPET et j'aimerais savoir selon vous quels sont les candidats pour ce types de technologies ? Y a-t-il une limitation au niveau de la taille ?

Prenons l'exemple de peptilligence d'Enteris biopharma : ils avaient sorti une courbe montrant la variation de la biodisponibilité absolue en fonction de la masse molaire. C'était une courbe de type exponentielle décroissante. Ce graphique montrait que pour des masses molaires inférieures à 1000, on pouvait s'attendre à des biodisponibilités entre 5 et 15 %, en étant optimiste, et des biodisponibilités beaucoup plus basses, de l'ordre de 2 à 3 %, pour des masses molaires comprises entre 3000/ 4000. Ce sont des résultats qu'ils avaient obtenus sur des chiens, pas chez l'homme. Souvent chez l'homme, on obtient des biodisponibilités beaucoup plus faibles que cela.

D'autres entreprises comme chiasma ont développé des « transient permeation enhancers ». Ce sont des peptides avec des stabilisants et un « permeation enhancer » dans une capsule liquide avec un enrobage entérique. Dans toutes les technologies, on retrouve presque systématiquement un système de délivrance entérique avec un revêtement soit d'un *tablet* ou d'une capsule. Ils ont également des stabilisants divers, des« enzyme inhibitors » et « absorption enhancers » comme des sels biliaires, de l'acylcarnitine, des acides gras, des acides aminés acylés comme Emisphere avec les SNAC.

Le peptide le plus souvent testé est la calcitonine. C'est le premier peptide qu'Enteris a développé. À l'époque, ils s'appelaient Unigene. Ils ont d'ailleurs fait faillite car la FDA avait émis un avis contre l'administration de calcitonine par voie orale. Ils ont connu une renaissance à travers Enteris BioPharma avec un modèle de développement un petit peu différent aujourd'hui. Ils détiennent toujours la calcitonine et je pense qu'ils travaillent aussi sur des analogues de la LHRH. Merrion avec GIPET travaillent beaucoup sur l'insuline avec Novo Nordisk qui a d'ailleurs racheté la technologie pour l'insuline et le GLP1. On retrouve également des analogues de la somatostatine.

En conclusion, on peut dire que les candidats sont surtout de petites molécules ?

Oui, ce sont des peptides avec des masses moléculaires comprises entre 500 et 3000 maximum.

On parle beaucoup de Rani therapeutics avec cette nouvelle approche d'injection intestinale. Qu'en pensez-vous ? Quelles seraient pour vous les limites de cette technologie ?

C'est une approche qui est très ingénieuse. Après, quelques questions restent à soulever, à savoir si cette approche ne pourrait pas entraîner des porosités, des faiblesses ou des détériorations locales de la paroi intestinale. Est-ce que cela pourrait favoriser l'entrée de pathogènes. Donc une approche intéressante mais aussi relativement complexe d'un point de vue fabrication, en particulier au niveau du ballon gonflable avec le couple acide citrique carbonate de sodium.

Il y aurait également certaines limitations au niveau de la dose délivrable : de 2 mg à 5 mg. Est-ce que c'est un facteur qui pourrait limiter le nombre de candidats pour cette technologie ?

Si la technologie permet une bonne biodisponibilité, une dose de 2 à 5 mg par jour, pour la majorité des peptides c'est largement suffisant. Souvent, la dose souhaitée pour un peptide est plutôt de l'ordre de 0.1 mg. Parfois, elle peut s'élever à 2, 3, 4 mg par jour, mais cela reste exceptionnel et c'est considéré comme une dose relativement élevée.

Et pour les protéines ?

Tout dépend de la protéine. Si on envisageait des anticorps monoclonaux, ça pourrait être différent, car les doses sont relativement élevées. Après, je ne suis pas convaincu que l'on veuille vraiment administrer des anticorps monoclonaux par voie orale. La majorité des biomédicaments, si on parle des hormones, cytokines, facteurs de croissance, pourraient être candidats.

Au niveau des technologies dont on a parlées, quelles sont les principales limites à leur commercialisation ?

Comme la biodisponibilité est relativement faible (sauf peut-être pour Rani mais Rani a d'autres complexité au niveau de la fabrication), le « cost of goods » risque d'être plus élevé. L'analogue de la somatostatine de Chiasma Octréotide voie orale versus l'injectable. Il faut administrer 20 mg en oral pour avoir la même pharmacocinétique que 0.1 mg par voie sous cutanée, soit une dose 200 fois plus élevée et donc une biodisponibilité de 0.5 %. Ce qui signifie qu'il faut être capable de produire la substance active. C'est bien différent et cela implique aussi de multiplier

ses capacités de production par 200: il y a donc une influence du coût final du produit, le « cost of goods » et le prix de revient du produit. C'est donc une difficulté majeure.

Pour un traitement par voie orale, il faut également montrer une supériorité pour pouvoir enregistrer. C'est de plus en plus difficile de convaincre les agences d'enregistrer un produit si on n'a pas une réelle supériorité par rapport au traitement existant. Dire que la voie orale c'est beaucoup plus pratique pour le patient plutôt qu'une injection, n'est pas suffisant. Il faut une supériorité qui peut être : une meilleur efficacité, un meilleur profil de safety/pharmacovigilance et là aussi, c'est une difficulté. C'est exactement cette difficulté qu'ont rencontré Chiasma avec MYCAPSA® dont la référence est une forme à libération prolongée. La FDA leur a demandé une phase III supplémentaire. Ce problème de supériorité efficacité par rapport aux formes existantes est quelque chose de réel.

De plus, la plupart des formes injectables ont des formes à libération prolongée avec une injection tous les 3 ou 6 mois. Est-ce qu'une administration quotidienne par voie orale est une réelle amélioration, est ce que c'est vraiment attractif ? Ce n'est pas sûr.

Avec tous ces constats et limites, selon vous, comment pourrait évoluer ce marché ?

Je pense que ces technologies présentent tout de même un intérêt. Il y a sans doute certaines pathologies pour lesquelles la diversité en termes d'arsenal thérapeutique est intéressante, notamment les pathologies lourdes comme le cancer, les maladies auto-immunes où la voie orale a un intérêt. Je pense que le choix des cibles est important. Je ne sais pas si l'octreotide et autres analogues de la somatostatine sont de bonnes cibles. Pour la calcitonine en revanche, c'était nécessaire ; malheureusement ça a été arrêté par la FDA. Le domaine du diabète est également intéressant car il existe un réel besoin de proposer un arsenal assez diversifié. Les malades peuvent se piquer plusieurs fois par jour, aussi l'intérêt est-il majeur.

Appendix D: Study questionnaire

Senior Director R&D of Bayer, who has 15 years of experience in the field of medical devices, filled this study questionnaire.

According to you, what is the ideal route of administration for a drug?

For me, transdermal is the ideal route. Anyone can put on a band-aid type patch. Not everyone can swallow pills easily; especially the elderly who may be required to take lots of pills. An injection is painful.

For biologics, which criteria are considered when choosing a drug delivery system?

The formulation is the key. The amount of drug that needs to be delivered and the frequency are also considered. The formulation may require the dose to be large so that may require a wearable delivery system. An injector is what is needed at this point. The selection of the type of injector depends on the amount of drug and the frequency of administration that is needed.

What are the main challenges of delivering biologics via injections?

The injection technology is very good. If you need a fast injection or slow injection or a device to deliver repeat injections, there are several companies who can provide that. Patient convenience needs to be considered when it comes to injection time. The injection technologies today can deliver a large range of viscosities and volumes. So the limiting factor is formulations.

What could be the advantages of delivering a biological drug orally?

Not having to do an injection is big. It would be great to replace injections with an oral tablet. Pharma companies would save millions by not having to train patients on how to use injection devices and by saving the cost of an injection device.

Do you know which technologies are currently developed to deliver biologics orally?

Yes **No**

If yes, which technology could have the greatest chance of success? Why?

I am not aware of any technology.

Appendix E: Intellectual property

Emisphere Technologies Inc., Cedar Knolls, NJ, US			
Publication Number	Title	Abstract	IPC Class
US20110178006A1 2011-07-21 EP2409569A2 2012-01-25 EP1478233A2 2004-11-24	Method for administering GLP-1 molecules	The invention relates to formulations that demonstrate the feasibility of oral absorption comprising glucose-like peptide-1 compounds and specified delivery agents, and to methods of stimulating GLP-1 receptor in a subject in need of such stimulation, by administration of the formulation of the present invention.	A01, A61, C07
Axcess Limited, Jersey, GB			
Publication Number	Title	Abstract	IPC Class
US7303762B2 2007-12-04 EP1326644B1 2006-07-05	Absorption enhancers	The invention relates to the use of hydrophilic aromatic alcohols to enhance the uptake of molecules, including biologically active macromolecules, into the body across the intestinal wall from the lumen of the gut; to compositions for oral administration which consists of an enteric capsule capable of withstanding transit through the stomach, containing a mixture comprising: (a) an active principal, and (b) a hydrophilic aromatic alcohol absorption enhancer; and to the use of the composition in medical treatment and diagnosis.	A61

US20150093419A1 2015-04-02	Absorption enhancers such as BHT, BHA or propyl gallate	The invention provides a pharmaceutical composition comprising a mixture of (a) an active macromolecular principle, and (b) an aromatic alcohol absorption enhancer chosen from butylated hydroxy toluene, butylated hydroxy anisole and analogues and derivatives thereof, wherein the aromatic alcohol absorption enhancer is present in an amount by weight greater than or equal to that of the active macromolecular principle, and further comprises a pharmaceutical composition comprising a mixture of (a) an active macromolecular principle, (b) an aromatic alcohol absorption enhancer chosen from propyl gallate, butylated hydroxy toluene, butylated hydroxy anisole and analogues and derivatives thereof, wherein the aromatic alcohol absorption enhancer is present in an amount by weight greater than or equal to that of the active macromolecular principle, and (c) a solubilisation aid capable of increasing the solubility of the aromatic alcohol absorption enhancer in aqueous media.	A61
CHIASMA INC, Newton, MA, US			
Publication Number	Title	Abstract	IPC Class
US20160193285A1 2016-07-07 WO2016094662A1 2016-06-16	Oral Octreotide administered in combination with other therapeutic agents	This invention relates to combination therapy of a subject suffering from acromegaly. The method of treatment comprises administration to the subject of a therapeutically effective amount of oral somatostatin receptor ligand (SRL) e.g. octreotide in combination with a therapeutically effective amount of a dopamine agonist and/or a growth hormone receptor antagonist and/or a selective estrogen receptor modulator (SERM) and/or a 2nd somatostatin receptor ligand (SRL).	A61, C07
US20160220628A1 2016-08-04 WO2016126830A1 2016-08-11	Method of treating diseases	Methods of treating acromegaly in a subject are described herein. Exemplary methods include orally administering to the subject at least once daily at least one dosage form comprising octreotide, wherein the octreotide in each dosage form is 20 mg, and wherein the administering occurs at least 1 hour before a meal or at least 2 hours after a meal.	A61

EP2343982A2 2011-07-20 WO2010032140A2 2010-03-25	Pharmaceutical compositions and related methods of delivery	The pharmaceutical compositions described herein include a suspension which comprises an admixture in solid form of a therapeutically effective amount of a therapeutic agent and at least one salt of a medium chain fatty acid and a hydrophobic medium, e.g. castor oil or glyceryl tricaprylate or a mixture thereof. The pharmaceutical compositions described herein contain medium chain fatty acid salts and are substantially free of alcohols. The pharmaceutical compositions may be encapsulated in a capsule. Methods of treating or preventing diseases by administering such compositions to affected subjects are also disclosed.	A61

Rani Therapeutics LLC, San Jose, CA,US

Publication Number		Title	Abstract	IPC Class
US20130165372A1 2013-06-27 US20150238571A1 2015-08-27 EP2726091A1 2014-05-07 WO2013003824A1 2013-01-03 US20150147390A1 2015-05-28	US20150023962A1 2015-01-22 US8764733B2 2014-07-01 US20160158516A1 2016-06-09 US20160144000A1 2016-05-26 US20160166650A1 2016-06-16	Therapeutic agent preparations for delivery into a lumen of the intestinal tract using a swallowable drug delivery device	Embodiments of the invention provide swallowable devices, preparations and methods for delivering drugs and other therapeutic agents within the GI tract. Many embodiments provide a swallowable device for delivering the agents. Particular embodiments provide a swallowable device such as a capsule for delivering drugs into the intestinal wall or other GI lumen. Embodiments also provide various drug preparations that are configured to be contained within the capsule, advanced from the capsule into the intestinal wall and degrade to release the drug into the bloodstream to produce a therapeutic effect. The preparation can be operably coupled to delivery means having a first configuration where the preparation is contained in the capsule and a second configuration where the preparation is advanced out of the capsule into the intestinal wall. Embodiments of the invention are particularly useful for the delivery of drugs which are poorly absorbed, tolerated and/or degraded within the GI tract.	A61, C07
WO2013003487A1 2013-01-03	EP2726141A1 2014-05-07	Device, system and methods for the oral delivery of therapeutic compounds		A61

US8846040B2 2014-09-30 US8809271B2 2014-08-19 US8809269B2 2014-08-19	US8969293B2 2015-03-03 US9259386B2 2016-02-16 US8980822B2 2015-03-17	Therapeutic agent preparations comprising etanercept, liraglutide, insulin, exenatide, somatostatin or somatostatin analogue, pramlintide for delivery into a lumen of the intestinal tract using a swallowable drug delivery device		A61, C07
US9283179B2 2016-03-15		GnRH preparations for delivery into a lumen of the intestinal tract using a swallowable drug delivery device		A61
US9149617B2 2015-10-06		Device, system and methods for the oral delivery of therapeutic compounds		A61
EP2515992A2 2012-10-31 US8721620B2 2014-05-13	WO2011079302A2 2011-06-30	Swallowable drug delivery device and methods of drug delivery		A61
US9457065B2 2016-10-04		Methods for delivering insulin preparations into a lumen of the intestinal tract using a swallowable drug delivery device		A61

Université de Bourgogne
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TITRE DE LA THÈSE : SYSTÈME DE DÉLIVRANCE DES BIOMÉDICAMENTS: INTÉRÊTS, ENJEUX ET IMPACT DE L'ADMINISTRATION PAR VOIE ORALE

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RESUMÉ :

Au cours des trois dernières décennies, les biomédicaments ont considérablement modifié l'arsenal thérapeutique en permettant de soigner des maladies qui ne disposaient pas de traitements satisfaisants jusqu'alors. Ces transformations au sein de l'industrie pharmaceutique sont également accompagnées par l'intensification de la recherche et du développement de ces médicaments. C'est ainsi que l'on compte maintenant plus de deux cents biomédicaments sur le marché. La haute spécificité associée à ces molécules découle de leur structure macromoléculaire complexe. Cette complexité structurale en fait également des produits particulièrement difficiles à formuler et à administrer. Aussi, la voie parentérale reste la voie la plus représentée pour cette classe pharmacologique. Cependant, la forte demande et l'intérêt croissant des investisseurs pour des biomédicaments oraux ont contribué au développement de nouveaux systèmes de délivrance qui pourraient avoir un impact important sur le marché. Les entreprises pharmaceutiques accordent beaucoup d'attention à ces travaux, en raison des avantages que de telles recherches peuvent fournir, qu'il s'agisse de reformulations de médicaments permettant leur repositionnement ou de l'obtention de nouveaux brevets permettant un monopole plus long sur le marché. L'objectif de ce travail est d'identifier et de présenter les enjeux clés relatifs à la délivrance des biomédicaments par voie orale. Les données recueillies permettent d'appréhender l'intérêt des technologies les plus avancées dans ce domaine ainsi que leurs impacts sur le marché des systèmes de délivrance, en particulier le marché des seringues pré-remplies.

MOTS-CLÉS : biotechnologie, industrie pharmaceutique, développement galénique, système de délivrance, biodisponibilité, voie parentérale, voie orale, excipients, biomédicament.